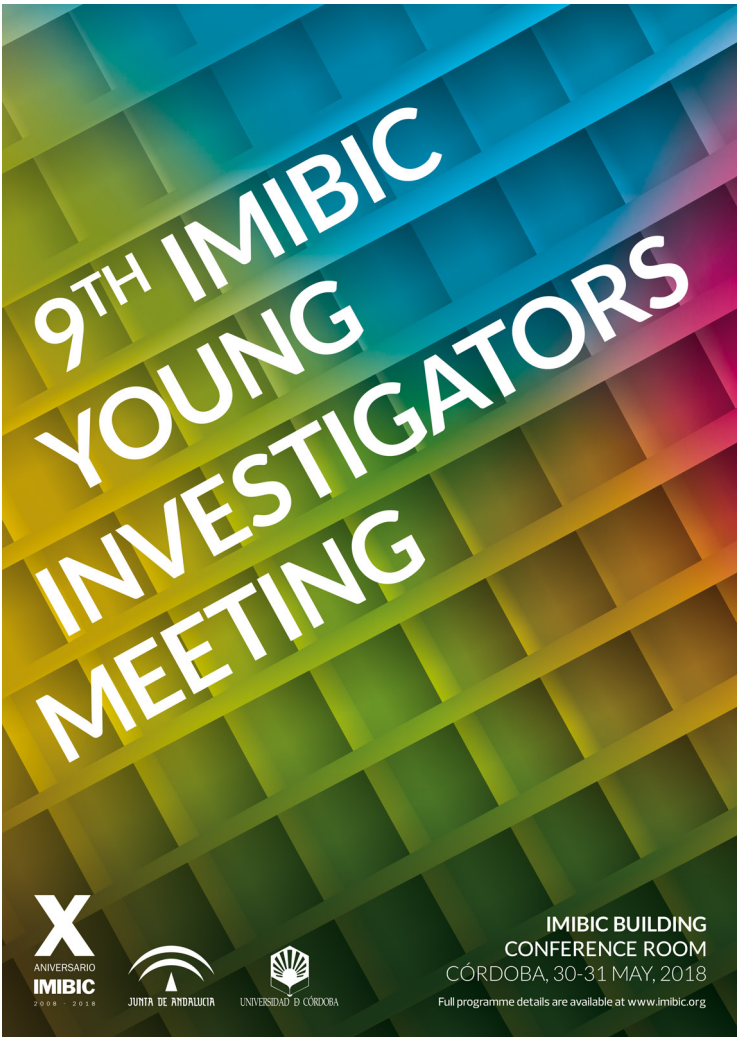
9TH IMIBIC YOUNG INVESTIGATORS MEETING

ABSTRACT BOOK

IMIBIC BUILDING
CONFERENCE ROOM
CÓRDOBA, 30-31 MAY, 2018


9TH IMIBIC
YOUNG
INVESTIGATORS
MEETING
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ANIVERSARIO
IMIBIC
2008 - 2018
JUNTA DE ANDALUCIA
UNIVERSIDAD D CÓRDOBA
IMIBIC BUILDING
CONFERENCE ROOM
CÓRDOBA, 30-31 MAY, 2018
Full programme details are available at www.imibic.org

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Acknowledgements
We thank the External Reviewers and the members of the Scientific Committee for their kind collaboration. We greatly acknowledge the Colegio de Médicos de Córdoba for its support and commitment to promote research among residents.

9th IMIBIC YOUNG INVESTIGATORS MEETING PROGRAMME

Day 1 (30th MAY)

08:10 – 08:40	**Registration and Poster display**
08:40 – 09:00	**Opening ceremony**
09:00 – 10:30	**SESSION I. Nutrition, Endocrine and metabolic diseases** **Chairs**: Mercedes Gil (Grupo GC23 IMIBIC) and José Antonio Bárcena (Grupo GC02 IMIBIC/UCO).
Ia. 09:00 – 09:15	Hormone secretion in neuroendocrine tumors: novel therapeutic options using 3D cell culture models. **Aura Dulcinea Herrera Martínez.**
Ib. 09:15 – 09:30	Effects of Kisspeptins in the control of metabolism. **Inmaculada Velasco Aguayo.**
Ic. 09:30 – 09:45	FGF23 impairs osteocyte maturation by inhibition of Wnt/b-catenin pathway and is associated with bone alterations in early CKD. **Juan Miguel Diaz Tocados.**
Id. 09:45 – 10:00	Postprandial response to the oral-fat tolerance test (OFTT) on plasma metabolomics profile. **María Asunción López Bascón.**
Ie. 10:00 – 10:15	Somatostatin receptor type 3: pharmacological and antitumor target for disease control of Non-functioning Pituitary Adenomas. **Mª Carmen Vázquez Borrego.**
If. 10:15 – 10:30	The Hypothalamic miR-30b/Mkrn3 Pathway is a Novel Central Regulator of Puberty Onset. **Violeta Heras Dominguez.**
10:30 – 11:00	**Coffee Break**
11:00 – 12:30	**SESSION II. Cancer (Oncology and Oncohematology)** **Chairs**: Yolanda Jiménez (Grupo GC03 IMIBIC) and Manuel Rodríguez (Grupo GC13 IMIBIC)
IIa 11:00 – 11:15	Antitumor effects of the splicing inhibitor Pladienolide-B in prostate cancer. **Juan Manuel Jiménez Vacas.**
IIb 11:15 – 11:30	SWATH-based quantitative proteomics in colorectal cancer reveals biological processes associated with immune evasion and metastasis in mesenchymal poor-prognosis tumors. **Rafael Manuel Jiménez Izquierdo**.

IIc 11:30 – 11:45	Bioinformatic Analysis of SILAC-Based Quantitative Proteome and Phosphoproteome for the identification of potential biomarkers for radiodermatitis associated with cancer radiotherapy. **Martín Garrido Rodríguez-Córdoba.**
IId 11:45 – 12:00	Potential therapeutic role of biguanides, statins and their combination in the treatment of prostate cancer. **Vicente Herrero Aguayo**.
IIe 12:00 – 12:15	Characterization of human dry sweat metabolome by gas chromatography and liquid chromatography coupled to mass spectrometry and evaluation of sampling protocols. **María del Mar Delgado Povedano.**
IIf 12:15 – 12:30	Metformin and Simvastatin in Combination: A Novel Potential High-Grade Astrocytomas Therapy. **Antonio Carlos Fuentes Fayos**.
12:30 – 13:30	**Plenary lecture. "Analyzing tumor genomes". Dra. Núria López-Bigas. Biomedical Genomics Group, Institut de Recerca Biomèdica (IRB) de Barcelona.**
13:30 – 15:00 – Lunch	
15:00 – 15:45	**Poster session I** **Chairs**: María Aurora Rodríguez Borrego (Grupo GA02 IMIBIC/UCO), Yolanda Almadén (Grupo GC13 IMIBIC) y Justo P. Castaño (Director Científico del IMIBIC).
15:45 – 17:15	**SESSION III. Chronic and Inflammatory diseases** **Chairs**: Alejandra Pera (Grupo GC01 IMIBIC) and Alvaro Arjona (Grupo GC18 IMIBIC)
IIIa. 15:45 – 16:00	Effect of magnesium on the processes of inflammation and oxidative stress associated with chronic kidney disease. **María Encarnacion Rodríguez Ortiz.**
IIIb. 16:00 – 16:15	Molecular profiling of frontal fibrosing alopecia reveals TH1/JAK-STAT upregulation without modulation of hair keratins. **Jesús Gay Mimbrera.**
IIIc. 16:15- 16:30	Analysis of the splicing machinery in leukocytes subsets from Rheumatoid Arthritis patients: potential role on the inflammatory, autoimmune and atherothrombotic profile. **Alejandro Ibáñez Costa.**
IIId. 16:30 – 16:45	Bile acid malabsorption in patients with chronic diarrhoea and Crohn's Disease or not. Value of 75SeHCAT in the diagnosis, evaluation of prevalence, response and tolerance to treatment. **Beatriz Gros Alcalde.**
IIIe. 16:45 -17:00	Systematic reviews of best methodological quality achieve low altmetrics when their abstracts are non-structured, low readable, and of poor reporting completeness. **Isabel Viguera Guerra.**

IIIf. 17:00 – 17:15	Rituximab induces an early re-assessment of the immune and vascular systems in patients with Systemic Lupus Erythematosus and Rheumatoid Arthritis. **María Luque Tévar.**
17:15 – 18:45	**SESSION IV. Infectious and Immunological diseases. Organ transplantation** **Chairs**: Eduardo Muñoz (Grupo GC04 IMIBIC/UCO) and Juan Muñoz (Grupo GC13 IMIBIC)
IVa. 17:15- 17:30	Selection of mutants of Klebsiella pneumoniae producing KPC-3 resistant to ceftazidime-avibactam and susceptible to carbapenems in patients treated with ceftazidime-avibactam. **Julia María Guzmán Puche.**
IVb. 17:30 – 17:45	Risk of infection and mortality among patients colonized with KPC-producing Klebsiella pneumoniae: validation of scores and proposal for management. Ángela **María Cano Yuste.**
IVc. 17:45 – 18:00	Tacrolimus-sparing immunosuppresion protocols in liver transplant patients with hepatocellular carcinoma. **Víctor Amado Torres.**
IVc. 18:00 – 18:15	Economic evaluation of the introduction in the vaccine schedule of 4CMenB (Bexsero®) in Spain. **Rafael Ruiz Montero.**
IVd. 18:15 – 18:30	Neonatal fecal biomarkers of necrotizing enterocolitis. **Cristina Pérez García.**
IVe. 18:30 – 18:45	Prognosis of urinary tract infections caused by colistin-resistant KPC-Klebsiella pneumoniae with high-level meropenem resistance. **Jorge Rodríguez Gómez.**

Day 2 (31th MAY)

08:30 – 09:00	**Registration and Poster display**
09:00 – 10:30	**SESSION V. Multidisciplinar** **Chairs**: Manuel Tena Sempere (Grupo GC10 IMIBIC/UCO) and Juana Serrano (Grupo GC16 IMIBIC)
Va. 09:00 – 09:15	Impact of Frailty in prognosis of very elderly patients with acute coronary syndrome. **Ernesto Martín Dorado.**
Vb. 09:15 – 09:30	Circulating GOAT enzyme as a novel biomarker for the diagnosis of significant prostate cancer. **Enrique Gómez Gómez.**
Vc. 09:30 – 09:45	Defective microRNA processing conferees the pathogenic role of neutrophils in rheumatoid arthritis. Modulation by ACPAs and inflammatory components and effects of biological therapies. **Iván Arias de la Rosa.**

Vd. 09:45 – 10:00	The combined use of tigecycline with high-dose colistin might not be associated with higher survival in critically ill patients with bacteraemia due to carbapenem-resistant Acinetobacter baumannii. **Tania Amat Serra.**
Ve. 10:00 – 10:15	Determination of primary fatty acid amides in different biofluids by LC–MS/MS: use of synthesized deuterated standards and study of sample preparation. **Laura de los Santos Castillo Peinado.**
Vf. 10:15 – 10:30	Clinical and analytical characteristics of patients with Crohn's disease with response to anti-TNF treatments. **Rosario Medina Medina.**
10:30 – 11:00	**Coffee Break.**
11:00 – 11:45	**Poster session II.** **Chairs**: María Aurora Rodríguez Borrego (Grupo GA02 IMIBIC), Yolanda Almadén (Grupo GC13 IMIBIC) y Justo P. Castaño (Director Científico del IMIBIC).
11:45 – 13:15	**SESSION VI. Nutrition, Endocrine and metabolic diseases** **Chairs**: Juan Solivera (HURS/IMIBIC) and Juan Antonio Vallejo (HURS/IMIBIC)
VIa. 11:45 – 12:00	Relevance of genetic background as a postprandial lipemia determinant in coronary heart disease patients: from the cordioprev study. **Juan Luis Romero Cabrera.**
VIb. 12:00 – 12:15	A higher intensity during physical activity practice seems to be associated with an increase in the prevalence of Normal-Weight in children. **José Manuel Jurado Castro.**
Vic. 12:15 – 12:30	Tetrahydrocannabinolic acid targets PPARg and prevents diet-induced obesity and metabolic syndrome. **Belén Palomares Cañero.**
VId. 12:30 – 12:45	Evaluation of novel pharmacogenetic tools for the activation of the Kiss1 neurons located in the arcuate nucleus. **Miguel Ruiz Cruz.**
VIe. 12:45 – 13:00	Growth hormone signals via Stat5b to suppress hepatic glucokinase and de novo lipogenesis. **Mercedes del** Río Moreno.
VIf. 13:00 – 13:15	Dietary pattern effect on endothelial dysfunction and vascular homeostasis in patients at risk of cardiovascular events: CORDIOPREV study. **María Magdalena Pérez Cardelo.**
13:15 – 13:30	**"My personal experience in science": Conversations between two emerging scientists. Nuria Barbarroja y Manuel Gahete.**
13:30 – 14:00	**Awards and Closing ceremony**

Description of the review process for selecting oral/poster presentations

Authors submitted their works through the Young Investigator abstract submission website from March 28th to April 15th. During the submission process, each author selected a specific scientific category (among the five IMIBIC Scientific Programs) and a preferred type of presentation (oral or poster).

At the deadline, a total of 112 abstracts were received. The distribution of abstracts by category was as follows:

- ***Active ageing and fragility:*** 12 abstracts, 1 as oral presentation and 11 as poster presentation.
- ***Nutrition, Endocrine and metabolic diseases:*** 36 abstracts, 16 as oral presentation and 20 as poster presentation.
- ***Infectious and Immunological diseases. Organ transplantation:*** 17 abstracts, 8 as oral presentation and 9 as poster presentation.
- ***Cancer (Oncology and Oncohematology):*** 23 abstracts, 8 as oral presentation and 15 as poster presentation.
- ***Chronic and Inflammatory diseases:*** 24 abstracts, 11 as oral presentation and 13 as poster presentation.

On April 16th, the Organization Committee distributed all abstracts received among 8 external reviewers during a face to face meeting without any information of authors, affiliation, etc. All reviewers were selected based on their distinguished scientific background and solid experience in evaluating research projects. The full list of the external reviewers can be found at the beginning of this book. External reviewers evaluated abstracts from April 19th to May 5th, scoring the communications between 0 and 5. ***It should be noted that the Organization Committee has not evaluated or scored any of the submitted abstracts***.

On May 9th, the Organization Committee held a new face to face meeting to distribute all abstracts evaluated into oral communications or poster presentations based on the score provided by the reviewers and the preference of selection of the participants (oral vs. poster). Of note, the Organization Committee tried to preserve the balance of scientific contents of each session and did not include more than 3 oral communications per session for the same research group. Thus, oral communications were divided in 6 sessions (6 communications/each), while poster presentations were distributed in 2 sessions (5 presentations/each). Considering the number of oral presentations submitted for each category, consistent with the IMIBIC Scientific Program, the Organization Committee decided to establish two sessions for *Nutrition, Endocrine and metabolic diseases*; one session for *Chronic and Inflammatory diseases*; one session for *Cancer (Oncology and Oncohematology)*; one session for *Infectious and Immunological diseases, and Organ transplantation*; and one multidisciplinary session, which includes different communications from the five categories.

Description of the review process for award selection

In order to motivate and boost high-quality presentations, IMIBIC establishes awards to the best oral presentation within each session. These awards will be selected based of the scores of the Scientific Committee, comprised by 2 scientific coordinators (translational and clinical) and all the chairs of the sessions (15 researchers), as well as by the scores of the external reviewers. The full list of members of the Scientific Committee, chairs and external reviewers can be found in this book. The Scientific Committee and Chairs will score every presentation from 0 to 5, taking into consideration the following criteria: (i) scientific quality of the work, (ii) presentation skills of the

presenter, and (iii) capacity to answer the questions raised by both the audience and moderators. The final score for each presentation will consist of the average of the score obtained by the Scientific Committee and chairs, and also the score provided by the external reviewers. The six highest scored oral presentations will compete for the Best Presentation Award of the Meeting. Presenters who were awarded in the last editions were excluded of the process.

To assess the poster presentations, three chairs of the IMIBIC/UCO will visit the 10 highest scored ones according to the external reviewers. They will be scored following the same criteria applied for oral presentations. The highest scored poster per session will be awarded.

ORAL COMMUNICATIONS
Abstracts

SESSION I
Nutrition, Endocrine and metabolic diseases

Ia. Hormone secretion in neuroendocrine tumors: novel therapeutic options using 3D cell culture models

Authors: *Aura D. Herrera-Martínez[1,2], Rosanna van Dungen[1], Fadime Dogan[1], Peter van Koetsveld[1], Justo P. Castaño[2], María A. Gálvez Moreno, Leo J. Hofland[1]*
Affiliations: 1 Department of Internal Medicine, division of Endocrinology, Erasmus MC, University Medical Center Rotterdam, the Netherlands. 2 Maimonides Institute for Biomedical Research of Cordoba (IMIBIC); Reina Sofia University Hospital Córdoba, Spain.

Symptoms control in functioning neuroendocrine tumors (NETs) may be difficult, thus, new therapeutic options are required. Since new in vitro tumor models seem to better mimic in vivo conditions, we aimed to study the effect of somatostatin (sst) and dopamine (D2R) receptor agonists (octreotide-OCT, cabergoline-CAB, respectively), sst-D2R multi-receptor targeting drugs (BIM065, BIM23A760) and the novel serotonin syntesis inhibitor telotristat, using 2D (monolayer) and 3D (spheroids) cultures. Methods: Human BON-1 and QGP-1 pancreatic NET cells were used. Dose-response studies in 2D and 3D cultures were performed in different medium conditions. The combination of telotristat and somatostatin analogs (octreotide and pasireotide) was assessed. DNA content, spheroid size, sst-D2R expression by qPCR, serotonin and CgA secretion were assessed. Results: Spheroid cultures of BON-1/QGP-1 allowed better cell survival in serum-deprived conditions, compared with 2D cultures and thus seem to appropriately mimic the growth pattern of PNET cells, especially in BON-1. OCT, CAB, BIM065, BIM23A760 and telotristat did not affect cell growth or spheroid size in BON-1/QGP-1 cultures. In BON-1 2D cells and spheroids, BIM23A760 and CAB/BIM065 respectively significantly inhibited CgA release in a dose-dependent manner. In BON-1 2D, CAB, BIM065 and BIM23A760 decreased serotonin release in a dose-dependent manner, in spheroids the effects were more potent. In QGP-1 spheroids, CAB and BIM065 decreased serotonin release. In addition, telotristat decreased serotonin release in a dose-dependent manner in both cell lines without affecting sst receptors expression. Only pasireotide 10-8M enhanced the effect of telotristat in BON-1 cells.

Conclusions: These results suggest that spheroids 3D cultures may be a promising method for evaluating cell proliferation and secretion in NET cell line models. The effects of sst-D2R multi-receptor targeting drugs on secretion appear predominantly mediated by D2R. Telotristat is a potent inhibitor of serotonin secretion in this pancreas model. Additional studies are required to confirm and extend these results.

Ib. Effects of Kisspeptins in the control of metabolism

Authors: *Inmaculada Velasco-Aguayo[1], Silvia León[2], Encarnación Torres[1], Violeta Heras[1], Alexia Barroso[1], María Jesús Vazquez[1], Manuel Tena-Sempere[1]*.
Affiliations: [1]Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC)/ Hospital Universitario Reina Sofia/ Universidad de Córdoba, Spain; Group: Hormonal Regulation of Energy Balance, Puberty and Reproduction. [2]Division of Endocrinology, Diabetes and Hypertension, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts.

Reproduction is an energy-demanding function, indispensable for perpetuation of the species. Reproductive capacity is subordinated to the magnitude of body energy stores and the metabolic state of the organism. Impaired energy homeostasis, in conditions such as anorexia or obesity, has a deleterious impact on the timing of puberty and is often associated to fertility problems. On the other hand, perturbed gonadal function perturbs also metabolic function.

Kisspeptins, encoded by the Kiss1 gene, have emerged in recent years as indispensable regulators of puberty and fertility by stimulating GnRH neurons, via their receptor Gpr54 (aka, Kiss1R). However, Kiss1 and Gpr54 are expressed in brain cells, other than GnRH neurons, and also in peripheral metabolic tissues including fat, liver or pancreas, which suggests that kisspeptins may have additional functions beyond reproduction.

To ascertain the putative role of kisspeptin signaling in the control of metabolism and energy homeostasis, we present herein the metabolic phenotyping of two mouse lines engineered to: (1) lack Gpr54 (and hence kisspeptin signaling) globally (Gpr54 -/-); or (2) lack Gpr54 in whole body except in GnRH neurons (Gpr54 -/- TG). While Gpr54-/- mice are profoundly hypo-gonadal, in the Gpr54-/- TG line, preservation of kisspeptin signaling in GnRH neurons maintains gonadal function. Our findings document that, while hypogonadism on itself has an important impact on metabolic homeostasis, kisspeptin signaling elsewhere than in GnRH neurons has also a discernible role in the control of metabolism, specifically as it concerns the regulation of food intake and glucose homeostasis. The metabolic actions of kisspeptins appear to be sexually dimorphic, with a clearer role in females. Recognition of the metabolic dimension of kisspeptin signaling may pave the way for the characterization of its pathophysiological roles, and eventual interest as therapeutic target, in highly prevalent metabolic conditions, such as obesity and type-2 diabetes.

Ic. FGF23 impairs osteocyte maturation by inhibition of Wnt/b-catenin pathway and is associated with bone alterations in early CKD

Authors: *Juan M. Díaz-Tocados[1,2,3,4], María E. Rodríguez-Ortiz[1,2,3,4], Yolanda Almadén[1,5,6], Julio M. Martínez-Moreno[1,2,3,4], Carmen Herencia[1,2,3,4], Noemi Vergara[1,2,3,4], Catarina Carvalho[7,8,9], João M. Frazão[7,8,10], Mariano Rodríguez[1,2,3,4], Juan R. Muñoz-Castañeda[1,2,3,4].*

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Chronic kidney disease (CKD) is associated with reduction of bone mineral density and fractures. In CKD patients, Fibroblast Growth Factor 23 (FGF23) is markedly increased. If there exist direct effects of FGF23 on bone cells is not clear. In this study, we investigated the effects of high FGF23 in bone using an experimental model of early CKD (hemi-nephrectomized rats) fed on a moderately high phosphate diet (1/2Nx-HP) as compared with Sham rats on the same diet. Additionally, in vitro studies were performed to assess the effects of recombinant FGF23 (rFGF23) on osteocytes and osteoclasts differentiation. In vivo, our results show that plasma FGF23 levels increased in Nx1/2-HP (454±50 vs 272±25; p<0.001) while other mineral metabolism parameters such as PTH, phosphate or calcitriol remained similar in both groups after 21 days. Bone histomorphometric analysis revealed that animals with higher plasma FGF23 concentration had decreased bone volume (21.4±1.77 vs 27.6±2.02; p<0.05) and increased bone turnover. In these animals, we also found that expression of specific osteogenic genes such as Runx2, Osterix or DMP1 was decreased while SOST expression (a canonical Wnt inhibitor) was increased in bone tissue. Consistently, plasma SOST levels resulted also increased in 1/2Nx-HP (198±12.1 vs 127±8.2; p<0.01). In vitro, high rFGF23 was added during mesenchymal stem cells differentiation into osteoblasts or for 24 hours once osteocytes were mature. Alkaline phosphatase activity and osteoblast master gene expression were decreased in rFGF23-treated cells. In mature osteocytes, high rFGF23 downregulated osteoblast genes expression such as Osterix, Osteocalcin, DMP1 and RANKL. Furthermore, high levels of rFGF23 decreased the nuclear translocation of ß-catenin after 24 hours. Respect to osteoclasts formation, rFGF23 enhanced TRAP staining, osteoclast enlargement, number of nuclei per osteoclasts and cathepsin K expression. In conclusion, high levels of FGF23 inhibit osteoblast maturation through inhibition of canonical Wnt signaling and increase osteoclast formation.

Id. Postprandial response to the oral-fat tolerance test (OFTT) on plasma metabolomics profile

Authors: *María Asunción López-Bascón[1,2,3,4] Mónica Calderón-Santiago[1,2,3,4], Antonio Camargo[1,5], José López-Miranda[1,5], Feliciano Priego-Capote[1,2,3,4]*
Affiliations: [1]Maimónides Institute for Biomedical Research (IMIBIC)/University of Córdoba/Reina Sofía University Hospital, Córdoba, Spain. [2]Department of Analytical Chemistry, University of Córdoba, Córdoba, Spain. [3]CeiA3 Agroalimentary Excellence Campus, University of Córdoba, Córdoba, Spain. [4] CIBER Fragilidad y Envejecimiento Saludable (CIBERfes), Instituto de Salud Carlos III, Spain. [5] CIBER Fisiopatologia Obesidad y Nutricion (CIBEROBN), Instituto de Salud Carlos III, Spain.

The physiological and biochemical human response to a meal is complex. In fact, postprandial response depends on many factors and involves multiple processes that include energy storage and metabolic switch in several organs such as liver, muscle and adipose tissue, accompanied by several compensating processes such as inflammation and oxidative stress. The oral-fat tolerance test (OFTT), which is based on an oral fat load administered to fasting people, has been widely used to assess the postprandial lipemia. Alterations in the physiological response to the OFTT can aid in the study of metabolic disorders.

The present research is focused on detecting changes in the concentration of plasma metabolites in the postprandial period after the OFTT, which consisted of a weight-adjusted meal with a preset composition. Plasma samples were collected from 200 patients of the CORDIOPREV study before and four hours after the intake of an OFTT meal. The OFTT meal consisted of a weight-adjusted meal with a fixed composition. Collected plasma samples were analyzed by LC–QTOF MS/MS and GC–TOF/MS in three different batches including 52, 116 and 32 individuals, respectively. A total number of 365 metabolites were tentatively identified by combination of both analytical techniques. The repeated-measures ANOVA led to the identification of 49 metabolites significantly altered ($p<0.05$) due to the OFTT. The significantly altered compounds were fatty acids and derivatives (19), bile acids and derivatives (13), carnitines (4), amino acids and analogues (2), benzene and substituted derivatives (2), carboxylic acids (2), phospholipids (2), steroids (2), endocannabinoids (1), glycerolipids (1) and prenol lipids (1). Special attention was paid to fatty acids, its derivatives and bile acids since these families comprises the 65% of significant metabolites. Changes in the fatty acids profile agreed with the OFTT composition while the pathways for biosynthesis of primary and secondary bile acids were also affected by the OFTT.

Ie. Somatostatin receptor type 3: pharmacological and antitumor target for disease control of Non-functioning Pituitary Adenomas

Authors: *Mari C. Vázquez-Borrego[1,2,3,4], Alejandro Ibáñez-Costa[1,2,3,4], Manuel D. Gahete[1,2,3,4], Álvaro Toledano-Delgado[1,3,5], Cristóbal Blanco-Acevedo[1,3,5], Rosa Ortega-Salas[1,3,6], Eva Venegas-Moreno[7], Alexandre Vasiljevic[8,9,10], Heather Hallen[11], Gérald Raverot[9,10,12], María A. Gálvez-Moreno[1,3,13], Alfonso Soto-Moreno[7], Marcelo Paez-Pereda[11], Michael D. Culler, Justo P. Castaño[1,2,3,4], Raúl M. Luque[1,2,3,4].*
Affiliations: [1]Maimonides Institute of Biomedical Research of Cordoba (IMIBIC), 14004 Cordoba, Spain. [2]Department of Cell Biology, Physiology and Immunology, University of Cordoba, 14004 Cordoba, Spain. [3]Reina Sofia University Hospital (HURS), 14004 Cordoba, Spain. [4]CIBER Physiopathology of Obesity and Nutrition (CIBERobn), 14004 Cordoba, Spain. [5]Service of Neurosurgery, HURS, 14004 Cordoba, Spain. [6]Anatomical Pathology Service, HURS, 14004 Cordoba, Spain. [7]Metabolism and Nutrition Unit, Hospital Universitario Virgen del Rocío, Instituto de Biomedicina de Sevilla (IBIS), 41013 Seville, Spain. [8]Faculté de Médecine Lyon Est, Université Lyon 1, Lyon F-69372, France. [9]INSERM U1052, CNRS UMR5286, Cancer Research Centre of Lyon, Lyon F-69372, France. [10]Centre de pathologie et de biologie, Groupement Hospitalier Est, Hospices Civils de Lyon, 69372 Lyon, France. [11]IPSEN Bioscience, Cambridge, 02142 Massachusetts, USA. [12]Fédération d'endocrinologie, Groupement Hospitalier Est, Hospices Civils de Lyon, Bron F-69677, France. [13]Service of Endocrinology and Nutrition, IMIBIC, HURS, 14004 Cordoba, Spain.

Non-functioning pituitary-adenomas (NFPAs) represent the most common type of pituitary-adenomas (PAs). NFPAs are mostly macroadenomas at diagnosis and are associated to severe comorbidities related to mass effect (i.e. headaches/visual defects). Trans-sphenoidal surgery is the mainstay of NFPAs treatment, although it is often not definitive, mainly due to the invasion of neighboring intracranial structures. Unfortunately, second-line treatment with somatostatin-analogs (SSAs), commonly used to treat functioning-PA (FPAs), have been largely ineffective in NFPAs, which might be explained by the limited expression of the main targets for SSAs [somatostatin-receptor subtypes-2 and 5 (*SSTR2*/*SSTR5*)]. However, since it has been previously shown that NFPAs present a predominant expression of *SSTR3,* the main aims of this study were: 1) to perform a comprehensive characterization of SSTR3 expression pattern (by quantitative-PCR and IHC) in NFPAs (n=71) compared to FPAs (n=80) and normal-pituitaries (NPs; n=12); and, 2) to determine the functional and therapeutic role of SSTR3 by analyzing different functional endpoints (i.e. cell-viability, apoptosis, chromogranin-A secretion, mRNA expression and intracellular-signaling pathways [western/blots and phospho-kinase array]) in response to SSTR3-agonists using primary NFPA cell-cultures and a preclinical mice-model developing NFPAs. Our results demonstrate that *SSTR3* was overexpressed in NFPAs compared to FPAs and NPs, and that SSTR3 expression was associated with relevant clinical parameters (i.e. LH levels). *In vitro* treatment with SSTR3-agonists reduced cell-viability and chromogranin-A secretion, increased apoptotic rate and altered the expression of key components in NFPA-cells, acting through the modulation/phosphorylation of several protein-kinases (i.e. MAPK, etc.). Interestingly, two NFPA-populations were found in response to cell-viability (responsive vs. unresponsive), being SSTR3 expression levels significantly higher in responsive NFPAs. Remarkably, treatment with a SSTR3-agonist reduced tumor-growth in the preclinical mouse-model. Altogether, this study demonstrates that SSTR3 plays a relevant therapeutic role in NFPAs, suggesting that pharmacological treatments targeting this receptor could be a promising therapeutic alternative in NFPAs.

If. The Hypothalamic miR-30b/Mkrn3 Pathway is a Novel Central Regulator of Puberty Onset

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Clinical and genetic data have recently revealed that *MKRN3*, a maternally imprinted gene encoding the makorin RING-finger protein 3, operates as potential repressor for the control of puberty; inactivating mutations of *MKRN3* have been recently reported as the first genetic cause of central precocious puberty. However, the molecular mechanisms for the biological actions and regulation of Mkrn3 in normal and altered puberty remain virtually unknown.

Based on our initial *in silico* analysis, which revealed the presence of three putative binding sites for the microRNA, miR-30b, at the 3'UTR of *Mkrn3* mRNA, we hypothesized that miR-30b would operate as regulator of Mkrn3, and thereby might contribute to the central mechanisms for the control of puberty in physiological and pathophysiological conditions.

We report here a series of expression and functional analyses addressing the role of such miR-30b/Mkrn3 pathway in the central control of puberty. Hypothalamic levels of Mkrn3 (mRNA and protein) markedly decreased during postnatal maturation before puberty, in both male and female rats, while miR-30b expression showed opposite expression profiles. Perturbations in pubertal development induced by neonatal exposure to high doses of estradiol benzoate (EB) or early postnatal underfeeding enhanced hypothalamic expression of Mkrn3 in pubertal and infantile female rats, respectively. Notably, hypothalamic miR-30b was suppressed in EB female rats. In line with the inverse miR-30b/Mkrn3 profiles, functional analyses documented a repressive action of miR-30b on Mkrn3 expression. In vitro assays, based on heterologous expression of a reporter vector harboring the 3'UTR of mouse Mkrn3 in HEK-293 cells, showed that miR-30b represses the transcriptional activity of *Mkrn3*. Moreover, intracerebroventricular administration to immature female rats of antisense-modified oligonucleotides (namely, Target Site Blocker, TSB-miR-30b) that selectively prevent miR-30b binding to the seed regions of this miRNAs at the 3'UTR of *Mkrn3* reversed the prepubertal down-regulation of Mkrn3 protein and delayed the onset of puberty.

Collectively, our findings unveil a novel hypothalamic miR-30b/Mkrn3 modulatory pathway with a prominent role in central control of puberty. Our data pave the way for a better understanding of the basis for altered puberty in conditions of metabolic stress and/or hormonal disruption.

SESSION II.
Cancer (Oncology and Oncohematology)

IIa. Antitumor effects of the splicing inhibitor Pladienolide-B in prostate cancer

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Prostate cancer (PCa) represents the tumor pathology with highest incidence among men in developed countries and its most aggressive phenotype [Castration Resistant Prostate Cancer (CRPC)] remains a lethal disease. CRPC seems to be associated to a dysregulation in the splicing process that leads to the generation of the aberrantly spliced androgen-receptor (AR) variant-7 (ARv7), which also confers resistance to CRPC treatments (Abiraterone and Enzalutamide). Consequently, the pharmacological modulation of the splicing process could represent a novel therapeutic avenue to treat PCa. Therefore, the aim of this study was to determine the direct effects of Pladienolide-B (a spliceosome inhibitor) in PCa cell-lines [androgen-dependent (LNCaP) and androgen-independent (22Rv1, DU145, PC3)] and in normal prostate cells (RWPE-1 cell-line and primary cell-cultures) by analysing different functional parameters of PCa aggressiveness (i.e. proliferation migration, apoptosis, etc.) and the expression of key markers of PCa aggressiveness and splicing machinery components (major/minor spliceosome and splicing factors). Pladienolide-B treatment was able to significantly reduce the expression levels of AR and ARv7 (mRNA and protein) in PCa cells. Notably, Pladienolide-B treatment decreased the proliferation of all PCa cell lines tested in a dose-dependent manner (100nM-0.01nM). These inhibitory effects were significantly less pronounced (100nM) in normal prostate-cells compared to that observed in PCa cell lines. Moreover, Pladienolide-B treatment also inhibited cell-migration, tumorospheres and colonies formation and the expression of key aggressiveness-markers [proliferation-markers (Ki67, PTTG), epithelial–mesenchymal transition markers (Vimentin), PCA3, etc.], and increased apoptosis rate in all the PCa cell tested. Interestingly, Pladienolide-B treatment dramatically altered the expression of several components of the spliceosome and splicing factors associated to PCa aggressiveness (e.g. SFPQ/KH-DRSB1/SRRM4/NOVA1/ESRP1/ESRP2). Taken together, our results demonstrate that Pladienolide-B clearly reduces PCa aggressiveness through the modulation of multiple functional and molecular regulatory layers, suggesting a potential novel therapeutic role of this compound in PCa and CRPC.

IIb. SWATH-based quantitative proteomics in colorectal cancer reveals biological processes associated with immune evasion and metastasis in mesenchymal poor-prognosis tumors

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The heterogeneity among patients with colorectal cancer (CRC) makes necessary to have personalized and more effective anti-tumor therapies for their treatment. Thus, recent studies have described different classifications based on gene expression signatures to characterize different molecular subtypes of CRC. These molecular classifications identify different CRC phenotypes, which confer a different behavior from the point of view of prognosis or response to specific treatments. On the other hand, the emergence of new proteomic methodologies, particularly data-independent acquisition (DIA) analysis-related approaches, would improve current gene expression based classifications of CRC. Therefore, the aim of this study was to identify protein expression signatures using SWATH-MS DIA and targeted data extraction, to aid in the classification of molecular subtypes of CRC and advance in the diagnosis and development of new drugs. For this purpose 40 samples of human colon adenocarcinoma and 7 samples of healthy tissue were subjected to proteomic and bioinformatic analysis. The proteomic analysis identified three different molecular CRC subtypes: P1, P2 and P3. Significantly, P3 subtype showed high agreement with the mesenchymal/stem-like subtype defined by gene expression signatures, and characterized by poor prognosis and low survival. The P3 subtype showed decreased expression of ribosomal proteins, the spliceosome, and histone deacetylase 2, as well as increased expression of osteopontin, SERPINA 1 and SERPINA 3, and proteins involved in wound healing, acute inflammation and complement pathway. This was also confirmed by immunodetection and gene expression analyses. Our results show that these tumors are characterized by alterations in the expression of proteins involved in processes and signaling pathways that are key determinants in the crosstalk between cancer cells and the host microenvironment, which in turn modulates immune evasion and the metastasis process, suggesting new therapeutic options in the treatment of this particularly aggressive type of CRC.

IIc. Bioinformatic Analysis of SILAC-Based Quantitative Proteome and Phosphoproteome for the identification of potential biomarkers for radiodermatitis associated with cancer radiotherapy

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Radiodermatitis is a secondary effect of the skin exposure to ionizing radiation and a limiting factor in the treatment of some types of cancer by radiotherapy. Since fibroblasts play a fundamental role in the pathophysiology of this disease, we decided to investigate the response of this cells to different doses of ionizing radiation at proteomic and phosphoproteomic level. Primary human fibroblasts proteome subjected to two different doses of radiation was labeled using a SILAC approach and analyzed by mass spectrometry for proteomics and phosphoproteomics. Through different bioinformatic resources in the R statistical programming environment, we developed different scripts to process and analyze the high amount of biological information contained in this type of data set. The analysis has covered the quality control of protein extraction, hierarchical clustering of SILAC ratios, significance test of the protein level changes, pathway analysis of the proteomic results and kinase activity estimation. The clustering results allowed us to see that there are not big differences between the global proteomic and phosphoproteomic profile of the cells under different treatments. The significance test has revealed that the changes produced at phosphopeptide level are bigger in both magnitude and significance than the ones produced at proteomic level. Finally, the output of the pathway analysis and the kinase activity estimation has resulted in altered biological processes that are concordant with the biological background of the disease, like the inflammatory process, the cell cycle control and the DNA repair pathway and other ones less studied in this context as the RNA splicing process and spliceosome formation. In conclusion, the bioinformatic analysis has allowed us to evaluate the changes produced from global biological processes to specific proteins and kinases and identify new therapeutic intervention targets for radiodermatitis associated with cancer radiotherapy.

IId. Potential therapeutic role of biguanides, statins and their combination in the treatment of prostate cancer

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Prostate cancer (PCa) is the most common tumor pathology in men worldwide and its development and progression are clearly conditioned by the metabolic status of the patient. Unfortunately, medical treatments currently used as first-line therapy after surgery fail to prevent the progression of the disease in a high percentage of cases and, therefore, new therapeutic tools to manage PCa are urgently needed. Biguanides and statins, two drug types commonly used in metabolism-related pathologies seem to exert antitumoral actions in several cancer types. Therefore, we aimed to determine the *in vitro* antitumoral capacity of biguanides, statins and their combination in human PCa-cells. To that end, the effects of different biguanides [metformin (5mM), buformin and phenformin (1mM)], statins [atorvastatin, simvastatin and lovastatin (10μM)] and selected combinations were tested in PCa-derived cell-lines ([androgen-dependent (LNCaP)) and androgen-independent (22Rv1, DU145, PC3)], and in normal prostate cells (RWPE-1 cell-line and normal primary cultures), by using different functional assays (i.e. proliferation/migration/apoptosis, etc.). Results revealed that all biguanides and statins reduced cell-proliferation in all the PCa cell-lines (except statins in DU145-cells), being the effect of phenformin and simvastatin significantly higher compared with buformin/metformin and lovastatin/atorvastatin, respectively. Interestingly, the combination of metformin with atorvastatin or simvastatin exerted a synergistic inhibitory effect on cell-proliferation. Of note, these inhibitory effects were significantly less pronounced in normal prostate cells compared to that observed in PCa cell-lines. Moreover, metformin, simvastatin and its combination significantly reduced cell-migration in PCa-cells, being this effect additive when both compounds were co-administrated in LNCaP/DU145-cells. Furthermore, the strong antitumoral effect of these compounds was reinforced with the results showing that combined treatment inhibited colony and tumorosphere formation. Altogether, our results demonstrate that biguanides and statins strongly reduce tumor aggressiveness features, being this effect significantly higher when these compounds are combined, suggesting a potential therapeutic role of these drugs, especially their combination, for the treatment of PCa.

IIe. Characterization of human dry sweat metabolome by gas chromatography and liquid chromatography coupled to mass spectrometry and evaluation of sampling protocols

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Fresh sweat has recently gained popularity as clinical sample in metabolomic analysis as this biofluid can be non-invasively sampled and its composition is modified by certain pathologies. In fact, human sweat has been recently used in metabolomic studies to discriminate between lung cancer patients and risk factor individuals. However, although sampling of dry sweat seems to be more stable than collection of fresh sweat because the former should be more reproducible, the whole composition of dry sweat is still unknown and there is a lack of strategies for its analysis, from collection to determination. With the final aim of characterizing the metabolome of dry sweat and comparing it with that of fresh sweat, two different sampling strategies for dry sweat (using a gauze or a paper, in both cases impregnated with different solvents) were evaluated by metabolomic analysis using GC–TOF/MS and LC–QTOF MS/MS. Three solvents were tested to check their influence on metabolites coverage. Among the tested strategies, paper with 50% (v/v) ethanol–phosphate buffer was the most suited option to obtain a representative snapshot of dry sweat metabolome. One hundred fifty-six compounds were tentatively identified by combination of the two platforms including interesting families of metabolites such as carnitines, sphingolipids and N-acyl-amino acids, among others. The comparison of the metabolomic profiles of fresh and dry sweat allows concluding that dry sweat is better for analysis of low polar metabolites while fresh sweat is more suited for polar compounds. As most of the identified metabolites are involved in key biochemical pathways, this study opens new possibilities to the use of dry sweat as source of metabolite biomarkers of specific disorders such as cancer. In fact, N-acetyl-amino acids such as acetylhistidine had been previously found at high-significantly lower concentration in urine from prostate cancer patients than in healthy individuals.

IIf. Metformin and Simvastatin in Combination: A Novel Potential High-Grade Astrocytomas Therapy

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High-grade astrocytomas are the most common adult central nervous system (CNS) tumor, glioblastoma multiforme (GBM-grade IV), and anaplastic astrocytoma (grade III) --a highly aggressive cancer with short median survival despite therapy. To date, surgery is the first line of treatment, combined with chemotherapy and/or radiotherapy, depending on various clinical factors. In contrast, the survival rate does not manage to overcome in the majority of patients two years after the diagnosis. Altogether is important take another way to tackle this pathology. In this sense, many drugs have demonstrated different pleiotropic effects including anti-tumoral actions. Among them are Metformin and Simvastatin currently prescribed to treat T2D patients and hypercholesterolemia, respectively. Both compounds seem to exert anti-tumoral actions individually in different tumor types through AMPK-dependent and -independent pathways. Thus, the aim of this study was to explore the individually and combination anti-tumoral effect of Metformin and Simvastatin on key functional parameters in human primary high-grade astrocytomas cell cultures and GBM cell lines (U87-U118). We observed, Metformin and Simvastatin individually, on cell proliferation was decreased significantly on primary cell cultures and U87-U118 at 48- and 72-h of incubation. Moreover, the combination treatment showed a novel additional anti-proliferative effect on cell proliferation. Further, Metformin, but not Simvastatin, reduced cell migration in the U118 at 6h, but not at 24h, of incubation, whereas, co-administration significantly reduced the migration capacity of U118 at both incubation times (6h and 24h). In addition, both drugs were able to modulate multiple signaling pathways and tumoral markers that could be involved in their anti-tumoral actions. Altogether, our novel results showed that metformin and simvastatin alone, and especially the combination treatment exert an anti-tumoral action found in this study, these safety compounds deserve to be further explored as novel potential therapeutic tools for the treatment of patients with high-grade astrocytomas.

SESSION III. Chronic and Inflammatory diseases

IIIa. Effect of magnesium on the processes of inflammation and oxidative stress associated with chronic kidney disease

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The development and progression of vascular calcifications (VC) is a prevalent complication in advanced stages of chronic kidney disease (CKD). Previous observations show that magnesium (Mg) may be beneficial in preventing the development of VC. Uremia is considered to be an inflammatory state, and both chronic inflammation and oxidative stress appear to have a causal effect in VC by affecting directly vascular smooth muscle cells (VSMC). The main goal of this work was to assess, through both *in vivo* and *in vitro* approaches, the effect of Mg on inflammation and oxidative stress associated with CKD.

In vitro studies were based on the culture of VSMC in the presence of high phosphorus (P), with or without Mg. *In vivo* experiments were performed in an experimental model of uremic rats (5/6 nephrectomy) feeding high P diet, injected with elevated doses of calcitriol and receiving Mg dietary supplementation.

VSMC incubated with high P exhibited an increase in pro-inflammatory mediators such as ICAM-1, inflammatory cytokines IL-1b, IL-6, IL8, and TNFa, and the levels of oxygen reactive species (ROS) that were associated with activation of NFkB. The addition of Mg at a concentration of 1.6 mM prevented the elevation in inflammatory markers, oxidative stress, and the activation of NFkB.

Uremic rats receiving normal dietary Mg (0.1%) showed elevated levels of ICAM-1 and high oxidative stress in terms of plasma peroxidase glutathione activity. By contrast, dietary Mg supplementation (0.6%) abolished all these processes.

Taken together, these results suggest the protective role of Mg in the generation of oxidative stress and inflammation in the context of renal disease, shedding light on the molecular mechanisms underlying this effect.

IIIb. Molecular profiling of frontal fibrosing alopecia reveals TH1/JAK-STAT upregulation without modulation of hair keratins

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Background: Frontal fibrosing alopecia (FFA) is a devastating, progressive scarring alopecia with worldwide increasing number of new cases and unknown pathogenesis, leading to lack of targeted therapeutics. Objective: To elucidate the molecular profile of scalp from patients with FFA. Methods: Scalp samples from patients with FFA (n=12) were compared with patients with alopecia areata (AA) (n=10) and control individuals (n=3). Gene expression of several immune mollecules were analyzed by PCR on scalp tissues and serum. FFA Severity Index [FFASI] was calculated for every patient. Results: Overall, FFA LS but also NL scalp showed higher induction of key TH1 markers (IFN-γ, CXCL9, CXCL10, p<0.05) as compared with both AA and controls. Several TH2/TH9 markers, such as IL-10 (p<0.01), CCL13 (p<0.01), IL-13, and IL-9 were upregulated in FFA lesions. S100A7, a TH17/TH22 marker upregulated in FFA lesional scalp (p<0.01), was also positively correlated with clinical disease severity (as measured by FFASI) in patients with more severe disease (r=, p<0.05). Key mediators of JAK-STAT signaling and T-cell activation (JAK3, STAT1, IL-2RA; p<0.05) were also significantly upregulated in FFA LS compared with controls and AA. Hair keratins did not show decreased expression in FFA, unlike in AA in which these characteristically downregulated genes (KRTAP1, KRT40, KRT75, KRT83, KRT84, KRT86) indeed showed decreased expression in AA scalp versus controls (p<0.05). Conclusion: Our data suggests that FFA is a highly inflammatory disease even in the non-lesional stage, with predominant TH1 and JAK-STAT pathway involvement and no associated suppression of hair keratins, the hallmark of AA. These findings identify a potential role for targeting JAK-STAT signaling in this debilitating disease.

IIIc. Analysis of the splicing machinery in leukocytes subsets from Rheumatoid Arthritis patients: potential role on the inflammatory, autoimmune and atherothrombotic profile

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The aim of this study was the identification in leukocyte subsets of Rheumatoid Arthritis (RA) patients of the alterations present in the splicing machinery, as well as their influence on the activity of the disease and its atherothrombotic profile.

We evaluated, using a microfluidic qPCR-array, a set of 45 elements of the splicing machinery in leukocyte subsets of 74 RA patients and 29 healthy donors (HD). In parallel, extensive clinical/serological evaluation, and correlation and association analyses were performed.

A significant alteration in several spliceosome components, mainly downregulated, was observed in the three leukocyte subsets from RA vs. HD. Remarkably, seven elements showed the same alteration pattern: a significant reduction in the three leukocyte subsets of RA patients except for U4atac, which was consistently over-expressed or virtually absent in HD leukocytes. Although this process needs further analysis, it is likely that the overexpression of U4atac could interfere in the normal functioning of the major spliceosome, thus altering the splicing of most introns (>99%), favoring non-canonical splicing, and generating aberrant proteins involved in the development of this pathology. Correlation and association studies showed a significant association between the expression levels of the 7 splicing factors cited and several clinical/serological parameters, including the activity of the disease, the positivity for anti-CCP and RF antibodies, and the expression of various inflammatory mediators. Likewise, reduced values of other splicing factors, differentially deregulated in the three leukocyte subtypes, were associated with radiological involvement, as well as with the presence of atheroma plaques, hyperlipidemia and hypertension.

Altogether, the generalized reduction of multiple elements of the splicing machinery and the consistent elevation of U4atac will deem necessary to examine its potential role on the alteration of the spliceosome, as well as its involvement in the regulation of key proteins expression in the pathology of RA.

IIId. Bile acid malabsorption in patients with chronic diarrhoea and Crohn's Disease or not. Value of 75SeHCAT in the diagnosis, evaluation of prevalence, response and tolerance to treatment

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Bile Acid Malabsorption (BAM) is a well-known disorder whose understanding is increasingly recognized. Proper diagnostic methods and treatments are emerging in the last decades, leading to a bigger relevance in clinical practice, although it is still underdiagnosed. Diagnosis is often based on response to BA sequestrants (e.g., cholestyramine or colesevelam) whilst the gold standard in Europe is 75SeHCAT. The diagnostic challenge behind diarrhoea symptom carries an important economic expense.
Methods: We analyzed retrospectively 61 patients with different gastrointestinal diseases (such as Crohn's Disease, cholecystectomy, Irritable Bowel Syndrome among others) and chronic diarrhoea, between August 2015 and October 2017. All presented BAM in the 75SeHCAT test, considering malabsorption as <10% abdominal retention at seventh day measurements. After BAM was confirmed by the test, cholestyramine was given to 56 of these patients, (5 were excluded due to an outbreak of their Crohn's Disease). Different doses were prescribed according to patient's tolerance, the most frequent dose used was 3gr/24 hours or 4gr/24 hours and maximum doses of 4gr/8 hours.
Results: A higher than expected incidence was found among the different groups. We studied the response to treatment and rate of discontinuation of 52 patients (4 patients were excluded because their answer to treatment has not been evaluated yet). Mean follow up was 5.8 months (2-12). Secondary effects were documented in 19.2% leading to reduction of the dose, change of the quelant or discontinuation. Response to first line was present in 71.2%, whilst 28.8% did not answer. From those non-responders, 33% quit the quelant afflicting secondary effects; 20% stopped the treatment and did not present secondary effect but second line was not prescribed; 13% did not refer side effects but decided to discontinuate, 33% were changed into a second or third line treatment. Finally global response including second and third line quelants was 76.9%.

IIIe. Systematic reviews of best methodological quality achieve low altmetrics when their abstracts are non-structured, low readable, and of poor reporting completeness

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Objectives: The aim of this study was to describe the relationship among abstract structure, readability, and completeness, and how these features may influence altmetrics results, considering the methodological quality of systematic reviews (SRs) about interventions in psoriasis. Study Design and Setting: Systematic literature searches about psoriasis interventions were under- taken on relevant databases. For each review, methodological quality was evaluated using the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) tool. Abstract extension, structure, readability, and quality and completeness of reporting were analyzed. Altmetrics, which consider Twitter and Facebook mention counts as well as Mendeley readers were obtained for each article. Analyses were conducted to describe any potential influence of abstract characteristics on review's social media diffusion. Results: We classified 139 intervention SRs as displaying high/moderate/low methodological quality. We observed that abstract readability of SRs has been maintained high for last 20 years, although there are some differences based on their methodological quality. Free-format abstracts were most sensitive to the increase of text readability as compared with more structured abstracts (IMRAD or 8-headings), yielding opposite effects on their quality and completeness depending on the methodological quality: a worsening in low quality reviews and an improvement in those of high-quality. Both readability indices and PRISMA for Abstract total scores showed an inverse relationship with altmetrics in high methodological quality reviews but not in those of lower quality. Conclusion: Our results suggest that increasing abstract readability must be specially considered when writing free-format summaries of high-quality reviews, because this fact correlates with an improvement of their completeness and quality, and this may help to achieve broader social media visibility.

IIIf. Rituximab induces an early re-assessment of the immune and vascular systems in patients with Systemic Lupus Erythematosus and Rheumatoid Arthritis

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Background/Purpose: This translational multicenter study explored changes in serologic variables following B-lymphocyte depletion by *in vivo* Rituximab (RTX) treatment in Systemic Lupus Erythematosus (SLE) and Rheumatoid Arthritis (RA) patients, and investigated RTX *in vitro* effects on the activity of other immune cells and on the vascular endothelium.

Methods: Sixteen SLE patients and sixteen RA patients treated with RTX were enrolled. Changes in circulating levels of inflammatory mediators, oxidative stress markers, and NETosis-derived products were evaluated at baseline and after 3 months. Serum miRNomes were identified using next-generation sequencing miRNA assay, and RTX-induced changes were delineated.

Purified lymphocytes from RA and SLE patients were treated *in vitro* with RTX. Serum from RA and SLE patients at baseline and after RTX therapy were further added to human umbilical vein endothelial cells (HUVECs), monocytes, and neutrophils purified from healthy donors and activity profiles were evaluated.

Results: *In vivo* treatment of SLE and RA patients with RTX caused a significant decrease of disease activity along with a prominent alteration in circulating biomolecules related to inflammation, oxidative stress and NETosis. Reversion in altered expression of miRNAs regulating those molecules was also noticed. Mechanistic *in vitro* analysis showed inhibition of NETosis and decline of the pro-inflammatory profiles of lymphocytes, monocytes, neutrophils and HUVECs after B-cell depletion.

Conclusion: This study provides evidence supporting an early RTX-induced re-assessment of the pro-inflammatory status -involving a re-establishment of the homeostatic equilibrium in the immune system and the vascular wall- thus paving the way to more tailored therapeutic approaches.

SESSION IV.
Infectious and Immunological diseases. Organ transplantation

IVa. Selection of mutants of Klebsiella pneumoniae producing KPC-3 resistant to ceftazidime-avibactam and susceptible to carbapenems in patients treated with ceftazidime-avibactam

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Background: Ceftazidime-avibactam (C-A) is used to treat infections caused by carbapenem resistant Enterobacteriaceae (CRE), including KPC-producing Klebsiella pneumoniae (KPC-Kp). KPC-Kp resistant to C-A but susceptible to carbapenems can be developed during treatment of CRE infections as a result of selection of blaKPC-3 gene mutations. Materials/methods: Pre- and post-therapy (Pre-Th, Post-Th) isolates from 13 patients treated with C-A for infections caused by KPC-3-producing Klebsiella pneumoniae (KPC-3-Kp) between 2014-2018 were examined. Antibiograms, modified carbapenemase-inactivation method (mCIM) and rep-PCR were performed in all the isolates. Mutations in the blaKPC-3 gene were studied by PCR and sequencing. Results: Pre-Th and Post-Th isolates presented an identical rep-PCR banding pattern, which was identical to that of the index KPC-3-Kp isolate from our hospital (ST512). Pre-Th isolates were resistant to all tested beta-lactams and carbapenems, susceptible to C-A and presented a positive mCIM. In 4 patients, Post-Th isolates showed resistance to C-A (MIC ≥256 mg/L), susceptibility to imipenem (MICs 0.125-0.75 mg/L) and meropenem (MICs 2-4 mg/L) and a negative mCIM test. In three of these patients Post-Th isolates presented a D179Y mutation in the blaKPC-3 gene and one of them presented an additional novel A172T mutation. In the fourth patient, another novel mutation was identified in the Post-Th isolate, arising from a 3-nucleotide loss and leading to the substitution of leucine-169 and asparagine-170 by histidine (LN169-170H). Conclusions: We report the selection of C-A-resistant, carbapenem-susceptible isolates in four patients treated with C-A for KPC-3-Kp infections. Three of the isolates showed D179Y mutation, previously associated with C-A resistance. Additionally we described two novels mutations namely LN169-170H and A172T, which may be also involved in C-A resistance. Selection of KPC-3-Kp mutants with an ESBL phenotype and susceptible to carbapenems has implications for surveillance programs of CRE and may impact clinical outcome in patients affected by these infections.

IVb. Risk of infection and mortality among patients colonized with KPC-producing Klebsiella pneumoniae: validation of scores and proposal for management

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Background: The management and indication of empirical treatment in *Klebsiella pneumoniae*-carbapenemase producing *K. pneumoniae* (KPC-Kp) colonized patients should be improved. Materials/methods: A prospective cohort of 94 patients colonized by KPC-Kp was followed for 90 days to validate: (i) the Giannella risk score (GRS) to predict the development of any type of KPC-Kp infection and (ii) the INCREMENT-CPE score (ICS) to predict 30-day mortality in patients with infection. Both scores were combined in order to recommend appropriate empirical treatment. The predictive ability of the scores was measured by calculating the area under the receiver operating characteristic (AUROC) curve. Results: The GRS showed an AUROC curve for infection due to KPC-Kp of 0.92 (CI 95%: 0.87–0.98). The optimal cutoff point was fixed at < 7 and ≥ 7 (92.9% sensitivity, 84.8% specificity); infection developed in 6.3% patients in the 0–6 GRS group and in 84.8% patient in the ≥ 7 GRS group. According to the ICS, the severity of the infection was also significantly higher in the ≥ 7 GRS group. The ICS showed an AUROC of 0.78 (95% CI: 0.65–0.91) for 30-day all-cause mortality among patients with infection. A CART analysis confirmed the GRS cutoff point at 7, and selected ≥ 12 points to predict a KPC- Kp infection with a high ICS. Conclusions: Our results validate the GRS and ICS for indicating empirical therapy in KPC-Kp-colonized patients. A management algorithm was developed.

IVc. Tacrolimus-sparing immunosuppresion protocols in liver transplant patients with hepatocellular carcinoma

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BACKGROUND: Tacrolimus minimization is central to prevent tumor recurrence in liver transplant (LT) patients with hepatocellular carcinoma (HCC). Tacrolimus may be combined either with everolimus or with mycophenolate for such purpose. We aimed to evaluate which combination allows for a lower tacrolimus exposure. METHODS: This is a case-control nested study within a prospective cohort of patients with HCC undergoing LT (FIS PI11/02867). Patients with HCC who underwent LT between 2012-2015 received a combination based on early-initiated everolimus (TAC+EVE group). Historical controls who received a combination with mycophenolate (TAC+MMF group) or tacrolimus monotherapy (TAC group) were selected by using propensity score matching (ratio 2:1). Tacrolimus trough concentrations within the first 18 months after LT were compared among the different groups (TAC+EVE vs TAC+MMF vs TAC) by using ANOVA. RESULTS: There were 192 patients included as follows: TAC+EVE (n=64, 33.3%), TAC+MMF (n=75, 39.1%) and TAC (n=53, 27.6%). There were no baseline differences regarding age (p=0.18), alcoholic cirrhosis (p=0.47) and serum creatinine (p=0.58). Hepatitis C was more prevalent in the TAC+EVE group. Mean tacrolimus trough concentrations within the first month after LT were significantly lower in the TAC+EVE group (7.11±2.3 ng/mL), as compared with TAC+MMF (9.43±3.3 ng/mL) and TAC (9.31±2.4 ng/mL); p<0.001. Tacrolimus trough concentrations were persistently lower in the TAC+EVE group: at 3 months (7.24ng/mL vs 9.02ng/mL; p=0.02), at 6 months (6.3 ng/mL vs 8.5ng/mL; p=0.001), at 12 months (5.6ng/mL vs 7ng/mL; p=0.049) and at 18 months after LT (4.3 ng/mL vs 6.9 ng/mL; p<0.001). Renal function was more effectively preserved in patients receiving everolimus during follow-up. There were no statistically significant differences in terms of biopsy-proven acute rejection rates (TAC+EVE 7.8% vs TAC+MMF 12.9% vs TAC 9.6%; p=0.62). CONCLUSIONS: Everolimus-based immunosuppression allows for a lower tacrolimus exposure and improved renal function in LT patients, without any effect on acute rejection rates.

IVd. Economic evaluation of the introduction in the vaccine schedule of 4CMenB (Bexsero®) in Spain

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Introduction: Bexsero®, a multicomponent serogroup B meningococcal vaccine (4CMenB), was licensed in Europe in January 2013. In Spain, despite MenB is the major cause of bacterial meningitis and trigger a social concern, Bexsero® is recommended and financed for patients at increased risk of invasive meningococcal disease but is not financed by the NHS in the routine vaccination schedule. Objectives: Evaluate the cost-effectiveness, epidemiological impact, and total costs of the introduction into the vaccination schedule to help inform vaccine policy in Spain. Methods: Adaptation to Spain of cost-effectiveness analysis (CEA), a deterministic decision-tree without herd effects. A cohort of new-born infants in 2015 has been modelled that have received two strategies: routine vaccination schedule with 4 doses of Bexsero® and non-vaccination. Costs are measured with a payer perspective and benefits in QALYs. 18 scenarios were evaluated to assess the robustness and the uncertainty of our model results. Spanish specific data were used where possible from routine surveillance data and literature. Results: In the base-case analysis routine infant vaccination prevents 54% of cases (31) and deaths (3) in the 0-4 years range and 29% of all cases and deaths in our cohort. The ICER was estimated to be 219,009 €/QALY. 86% of the costs in the vaccination strategy of 118 M € are caused by the vaccine dosis price. Conclusions: Given current meningococcal epidemiology in Spain and the available data of the vaccine, our model shows that the routine vaccination with Bexsero® is not cost-effective. Only with a very low vaccine dosis price (< 5.6 €) could it be recommended based on efficiency criteria.

IVe. Neonatal fecal biomarkers of necrotizing enterocolitis

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INTRODUCTION: Necrotizing enterocolitis (NEC) is the leading cause of gastrointestinal morbidity and mortality in premature infants. The pathophysiology of NEC remains incompletely understood. It is presumed to involve bacteria translocation through immature intestinal epithelium defense barriers, leading to tissue invasion and damage. Since early symptoms of NEC are often rather non-specific, its diagnosis can be difficult. Therefore, the search for diagnostic inflammatory markers for NEC remains warranted. These biomarkers must be non-invasive and they should be fast, easy and inexpensively detected. Stool samples are an ideal way to search biomarkers. Myeloperoxidase (MPO) and alkaline phosphatase (AP) are typical inflammatory intestinal markers but their use as non-invasive ones has not been much studied. Since MPO and AP are enzymes, their activity is cost-effective and easily quantifiable. Fecal calprotectin has been extensively used as a biomarker in gastrointestinal diseases.

OBJECTIVE: To evaluate fecal MPO and AP activity in children as possible non-invasive intestinal inflammation biomarkers.

METHODS: MPO and AP activity in meconium of term (AT, n = 21) and preterm (PT, n = 26) newborns and in stool samples of children suffering from NEC (NEC, n = 9) hospitalized in the neonatal intensive care unit (NICU) of our hospital were analyzed. MPO and PA activity were obtained by spectrophotometry and calprotectin concentration by ELISA.

RESULTS: MPO activity and calprotectin levels were higher in the NEC group compared with the two other. In addition, they were moderate higher in PT group regarding the AT group. We did not find significant variations in PA activity.

CONCLUSION: Since the severity of this disease is acknowledged, searching for biomarkers for NEC early diagnosis and evolution prognosis is a current research priority. This preliminary study emphasizes that fecal MPO activity may be a good and early NEC marker.

IVf. Prognosis of urinary tract infections caused by colistin-resistant KPC-Klebsiella pneumoniae with high-level meropenem resistance

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Materials/methods: This is a retrospective observational study of patients with UTI due to *K. pneumoniae* diagnosed from December 2012 to October 2015. The objectives of theses study are: (i) to assess whether UTIs caused by an epidemic KPC-Kp strain is associated with poorer outcome , clinical-microbiologic cure (CMC) and 30-day all-cause mortality, than carbapenem-susceptible isolates; (ii) in the KPC group, whether combined targeted therapy (gentamicin plus fosfomycin) is associated with better outcome. For statistical analysis, a multivariable analysis was used to study the association of KPC-Kp with clinical-microbiologic cure (logistic regression) and 30-day all-cause mortality (Cox regression). The association of combined targeted therapy with outcome was also analyzed in patients with UTI caused by KPC-Kp including a propensity score for receiving combination targeted therapy. Results: Overall, 134 patients were included; 40 cases (29.9%) were produced by KPC-Kp resistant to colistin and with high-level resistance to meropenem (MIC ≥ 64 mg/L) . While in the univariate analysis there was a statistical association between KPC-Kp and lower probability of CMC (OR, 0.40; 95% CI, 0.18 - 0.90), was not independently associated in the multivariate analysis (adjusted OR, 0.51;95% CI, 0.19-1.34). KPC-Kp etiology could not be shown to be associated with 30-day all-cause mortality (adjusted HR,1.81, 95% CI, 0.73-4.5). Among UTI by KPC-KP, CMC for combined targeted therapy was 81.8% (9/11) and 51.7% (15/29) for monotherapy. In univariate and multivariate analysis, the type of targeted therapy (combined/monotherapy) was not associated with a worse CMC. Crude OR 4.2, 95%CI 0.77-22.91; adjusted OR 7.09, 95% CI,0.79-63.41. Nevertheless, an association cannot be discarded (low precision of the estimation, wide CI). Combination targeted therapy was not associated with lower mortality (adjusted HR,0.61; 95% CI. 0.13-2.85). Conclusions: Despite the low precision of the estimates, KPC-Kp did not seem associated with poorer outcome in patients with UTI, and combination therapy might not be needed in all cases. Fosfomycin or gentamcin, in mono or combined therapy of both, seems effective in patients with UTI due to KPC-Kp.

SESSION V.
Multidisciplinar

Va. Impact of Frailty in prognosis of very elderly patients with acute coronary syndrome

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Background: Information about the impact of frailty in patients with acute coronary syndromes (ACS) is scarce. No study has assessed the prognostic impact of frailty as measured by the FRAIL scale in very elderly patients with ACS. Methods: The prospective multicenter *LONGEVO-SCA* registry included unselected patients with ACS aged 80 years or older. A comprehensive geriatric assessment was performed during hospitalization, including frailty assessment by the FRAIL scale. The primary endpoint was mortality at 6 months. Results: A total of 532 patients were included, 20 of them by our center. Mean age was 84.3 years, 61.7% male. Most patients had positive troponin levels (84%) and high GRACE risk score values (mean 165). A total of 205 patients were classified as pre-frail (38.5%) and 145 as frail (27.3%). Frail and pre-frail patients had a higher prevalence of comorbidities, lower left ventricle ejection fraction and higher mean GRACE score value. A total of 63 patients (11.8%) were dead at 6 months. Both pre-frailty and frailty were associated with higher 6-month-mortality rates (p<0.001). After adjusting for potential confounders, this association remained significant (HR 2.71; 95% CI 1.09-6.73 for pre-frailty and HR 2.99; 95% CI 1.20-7.44 for frailty, p=0.024). The other independent predictors of mortality were age, Charlson Index and GRACE risk score. Conclusions: The FRAIL scale is a simple tool that independently predicts mortality in unselected very elderly ACS patients. The presence of pre-frailty criteria should also be taken into account when performing risk stratification of these patients.

Vb. Circulating GOAT enzyme as a novel biomarker for the diagnosis of significant prostate cancer

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Prostate cancer (PCa) is one of the main tumor pathologies in men but the diagnostic tools are limited by the lack of appropriate biomarkers as PSA (the current gold-standard) which displays a poor specificity/sensitivity. In this scenario, we recently demonstrated that GOAT-enzyme is significantly elevated in PCa-tissues and in blood-samples from PCa-patients compared with healthy-controls, using a small patients cohort. Therefore, our objective was to further explore the potential of GOAT to improve PCa-diagnosis using an ample patients cohort (n=312) and defining subgroups that could benefit from this biomarker. Specifically, patients included: 1) healthy-volunteers (controls presenting low PSA-levels; n=65); 2) another control-population presenting high PSA-levels that underwent prostate-biopsy but with negative result (pathology-analysis; n=64), and; 3) patients with PCa (positive biopsy; n=183). Participants provided blood in the morning under fasting-conditions. Plasma GOAT levels were evaluated by commercial-ELISA. Statistical analysis to build the ROC-curves were performed using DeLong-tests. Our results confirmed that GOAT levels were significantly higher in patients with PCa vs. control-patients, and in those with significant-PCa [Gleason Score (GS)≥7] compared to the non-significant PCa-group (controls and PCa with GS<7; $p<0.01$). Furthermore, GOAT levels positively correlated with GS ($r=0.24$; $p=0.001$). The association of GOAT levels with the diagnosis of significant-PCa was independent from usual clinical variables [i.e. PSA/age/DRE, etc.; OR of 1.007 (1.002-1.012); $p<0.01$]. Interestingly, GOAT outperformed PSA in patients with PSA levels ranging 3-20ng/ml (the critical range to detect false positives and negatives with PSA-test) for the diagnosis of significant-PCa [GOAT: AUC=0.612 vs. PSA: AUC=0.494]. Finally, a panel of key PCa variables combining age/DRE/testosterone with GOAT outperformed the same panel but with PSA [AUC=0.720 vs. AUC=0.705; $p<0.001$, respectively]. Therefore, our results confirm that GOAT might be used as a non-invasive, complementary, biomarker for the diagnosis of significant-PCa in patients at high risk of PCa (with PSA<20ng/ml).

Vc. Defective microRNA processing conferees the pathogenic role of neutrophils in rheumatoid arthritis. Modulation by ACPAs and inflammatory components and effects of biological therapies

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Objectives: 1) to investigate the miRNA expression pattern in neutrophils in rheumatoid arthritis (RA) and its contribution to the pathogenic profile of these cells 2) to analyze the effect of the antibodies to citrullinated protein antigens (ACPAs) or inflammatory components and its modulation by biological therapies (anti-TNFa/Infliximab (IFX) or anti-IL6R/Tocilizumab (TCZ)).
Methods: neutrophils were isolated from peripheral blood of 40 healthy donors and 40 RA-patients, and paired synovial fluid of 20 RA-patients. nCounter microRNA Assay was used to detect 800 microRNAs. Healthy-neutrophils were treated in vitro with ACPAs or TNFa or IL-6. In vitro treatment of RA-neutrophils with TCZ and IFX, was also carried out. Transfection with pre-miRNAs was performed in RA-neutrophils. DICER gene was silenced by lentiviral vector in neutrophils.
Results: RA-neutrophils showed a global downregulation of the miRNAs and genes involved in miRNA biogenesis, alongside with an upregulation of their mRNA targets involved in survival, migration and inflammation. Decreased levels of miRNAs and DICER inversely correlated with autoimmunity, inflammatory clinical parameters and disease activity. ACPAs or TNFa decreased the expression of the miRNAs, genes involved in their biogenesis and increased their mRNA targets. IFX was able to reverse the expression of miRNAs and genes involved in their biogenesis. Transfection with the pre-miRNAs-223, -126 and -148a specifically modulated genes regulating inflammation, survival and migration. DICER depletion influenced the inflammatory profile of the neutrophil, increasing the expression of numerous cytokines.
Conclusions: 1) RA-neutrophils exhibit a defect in the miRNAs processing, inducing an alteration of numerous genes involved in inflammation, survival and migration, and being induced by ACPAs and TNFa. 2) IFX reduces the proinflammatory pattern of RA-neutrophils through the restoration of the miRNA biogenesis. 3) miRNA-223, miRNA-126 and miRNA-148 are modulators of key genes involved in the pathogenesis of RA-neutrophils. 5) Inflammatory status in neutrophils is directly regulated by DICER.

Vd. The combined use of tigecycline with high-dose colistin might not be associated with higher survival in critically ill patients with bacteraemia due to carbapenem-resistant Acinetobacter baumannii

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Objective. To assess the association of survival and treatment with colistin and tigecycline in critically ill patients with carbapenem-resistant Acinetobacter baumannii bacteraemia.
Methods. An observational cohort study was carried out. Targeted therapy consisted of monotherapy with colistin (9 million UI/day) or combined therapy with colistin and tigecycline (100 g/day). The primary outcome was 30-day crude mortality. The association between combined targeted therapy and mortality was controlled for empirical therapy with colistin, propensity score of combined therapy and other potential confounding variables in a multivariate Cox regression analysis.
Results. A total of 118 cases were analysed. Seventy-six patients (64%) received monotherapy and 42 patients (36%) received combined therapy. The source of bacteraemia was primary in 18% (21/118) of the patients, ventilator-associated pneumonia in 64% (76/118) and other sources in 14% (16/118). The 30-day crude mortality rate was 62% (42/76) for monotherapy and 57% (24/42) for combined therapy. The variables associated with 30-day crude mortality were: Charlson index (hazard ratio (HR) 1.16, 95% CI 1.02–1.32; p 0.028), empirical therapy with colistin (HR 2.25, 95% CI 1.33–3.80; p 0.003) and renal dysfunction before treatment (HR 1.91, 95% CI 1.01–3.61; p 0.045). Combined targeted therapy was not associated with lower adjusted 30-day crude mortality (adjusted HR 1.29, 95% CI 0.64–2.58; p 0.494).
Conclusions. Combined targeted therapy with high-dose colistin and standard dose tigecycline was not associated with lower crude mortality of bacteraemia due to carbapenem-resistant A. baumannii in critically ill patients.

Ve. Determination of primary fatty acid amides in different biofluids by LC–MS/MS: use of synthesized deuterated standards and study of sample preparation

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Contribution of primary fatty acid amides (PFAMs) to a wide variety of biological processes –such as analgesic and antianxiety activity, sleep induction, increased food uptake and alcohol consumption, among others– has aroused interest in recent years with the progress made toward understanding their metabolism. Currently, it has been elucidated that metabolic alterations are associated with neurodegenerative disorders. Particularly, Alzheimer's disease produces a reduction of fatty acid amides; therefore, these compounds could be potential biomarkers for early diagnosis. These bioactive lipids are normally detected at nanomolar levels in complex matrixes, making their detection and identification challenging. Therefore, a method for quantitative analysis of seven PFAMs (lauramide, myristamide, linoleamide, palmitamide, oleamide, stearamide and behenamide) in human urine, plasma, saliva and sweat is reported in this research. The method was based on analysis of these biofluids by liquid chromatography coupled with tandem mass spectrometry. Two sample preparation steps were compared to test their efficiency on each biofluid: solid-phase extraction (SPE), and dilution with protein precipitation, if required. Detection of the seven metabolites was performed by multiple reaction monitoring (MRM) mode, and quantitative analysis was supported on the use of isotopically stable labeled internal standards in the calibration method, which required the synthesis of each internal standard since they were not commercially available. Detection limits for the target analytes were within the range 0.3–3 ng mL^{-1}. The method was applied to urine, plasma, saliva and sweat from male and female volunteers to estimate the concentration profiles as a function of sex and the target biofluid. The analytical features of this method supported its applicability in clinical studies aimed at elucidating the role of PFAMs metabolism.

Vf. Clinical and analytical characteristics of patients with Crohn's disease with response to anti-TNF treatments

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Background and aims: Nowadays, Crohn's Disease (CD) is one of the most prevalent inflammatory bowel diseases (IBD) in Europe (~70 cases/100,000 inhabitants). There is no cure, and therefore, the primary goal of treatment is to induce and maintain remission and to prevent omplications. Current therapies include anti-tumor necrosis factor (TNF). Some patients may not have an initial response to these drugs, and others will develop loss of response over time. In addition, sometimes they have adverse effects and treatments are often expensive. For these reasons, it is necessary to identify some predictor factors of response. Methods: 54 CD patients, naïve to anti-TNF therapy were enrolled, from 2014. Demographic, analytical, nutritional and physiopathology data have been collected during the first year of treatment. Results: Most of the patients (77.3%) showed a sustained response (SR) after the first year of treatment. However, 4.5% of patients had not initial response (NIR) at 3 months of treatment, and 18.2% of patients lost response (LR) during the first year. We have identified as factor of non-response, the necessity of anti-TNF treatment in patients with recent diagnosis (< 12 moths) (years from diagnosis to anti-TNF treatment NIR: 0±0 vs LR: 9.9±5.9 and SR: 6.32±8.0), and high levels of leucocytes before treatment (NIR: 13.7±2.1 vs LR: 8.4±2.3 and SR: 7.6±2.9). In addition, we have identified the overweight as a factor of losing response during the first year of treatment, independently of type of anti-TNF (BMI: NIR: 24.5±7.5, LR: 27.6± 4.6 vs SR: 23.4±3.6).
Conclusions: Early use of anti-TNF and high levels of leucocytes, probably related to a severe disease, are associated with a non- primary response. In addition, overweight is associated with losing of response to anti-TNF. These results highlight, the necessity of new biomarkers of response to anti-TNF to improve the treatment of patients with CD.

SESSION VI.
Nutrition, Endocrine and metabolic diseases

VIa. Relevance of genetic background as a postprandial lipemia determinant in coronary heart disease patients: from the cordioprev study

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Introduction: Postprandial lipemic response (PPLr) is considered as an independent factor for cardiovascular disease (CVD). Objective: To develop a genetic risk score (GRS) with a cluster of single nucleotide polymorphisms (SNPs) related with triglyceride (TG) metabolism in order to predict an undesirable PPLr in a population with established CVD. Material and Methods: Genotyping and fat tolerance test (FTT) were performed at baseline in 1,002 patients included in the CORDIOPREV study (NCT00924937). We selected 41 SNPs previously related with TG metabolism and PPLr. The FTT were performed with fatty food meal with 0.7 g fat/kg body weight (12% saturated fatty acid [SFA], 10% PUFA, 43% MUFA), 10% protein and 25% carbohydrates. Blood samples for biochemical testing were collected before the meal and every hour during the next 4 h. We analysed these SNPs in relation with an undesirable PLR (≥ 220mg/dL at any time after a FTT). Results: We computed a weighted-GRS with the estimates odds ratio (OR) for each risk allele in SNPs selected. Overall population were grouped in tertiles of GRS. Significant differences were observed in PPLr between tertiles of GRS measured as the postprandial triglycerides response (TG; p = 0.003) and chylomicrons (QM; p = 0.019). On the other hand, the area under the curve (AUC) of TG (p = 0.001) and QM (p = 0.019) were differents between tertiles of GRS. Conclusions: Our findings suggest that that cumulative genetic of TG SNPs grouped in a GRS could predict an undesirable PPLr in coronary heart disease patients allowing us consequently identify those patients with an increased CVD risk.

VIb. A higher intensity during physical activity practice seems to be associated with an increase in the prevalence of Normal-Weight in children

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Background: A low practice of physical activity (PA) and high levels of sedentarism are associated with unhealthy states in children. The aim is to evaluate the relations between the different levels of PA, as well as with the classification by BMI among children with different growing stage.
Material and method: A descriptive study was carried out in 633 pre-pubertal and pubertal children. An anthropometric assessment was realized to classify them into normal-weight, overweight and obesity by Cole, 2004. The participants wore an Actigraph model accelerometer for at least 3 days (being one of them at weekend) and a minimum of 8 hours, in order to quantify the level of PA practice. A pairwise comparison was made by Kuskal Wallis test and correlations by Spearman test.
Results: An inverse relation was found between all PA levels and the sedentarism (P<0.001) and positive among the different PA levels in children, mainly between moderate and vigorous PA (r=0,642). In addition, an inverse relation was showed between vigorous-PA and the BMI z-score (P=0.003), remains only at prepubertal stage (P = 0.004) when it was studied by both growing stage. According to the classification by Cole, the overweight group and obese group showed less sedentary time than the normal-weight group (P=0.001 and P=0.002, respectively). However, the normal-weight group showed higher number of minutes of vigorous PA than obese group (P=0.003). This difference was not found at pubertal stage.
Conclusions: Obese children seem to have a more active lifestyle, although sedentary lifestyle has been described in children with higher BMI. Perhaps the key is that obese children should increase vigorous activity trying to reduce their BMI, specially in adolescents.

VIc. Tetrahydrocannabinolic acid targets PPARγ and prevents diet-induced obesity and metabolic syndrome

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Medicinal cannabis is a therapy that has garnered world-wide attention in recent years, with millions of patients benefiting from it. Phytocannabinoids, the active compounds, are produced in the plant in acidic form and are decarboxylated upon heating. While the biological effects of decarboxylated cannabinoids such as Δ^9-tetrahydrocannabinol (Δ^9-THC) have been extensively investigated, the bioactivity of Δ^9-THCA is largely unknown. Remarkably, Δ^9-THCA is not psychotropic and shows potent PPARγ agonistic activity. PPARγ is a nuclear receptor able to regulate lipid turnover and metabolism. Herein, we have investigated the role of Δ^9-THCA on PPARγ modulation and its efficacy in a murine model of metabolic syndrome.

We found that Δ^9-THCA mediated ubiquitination and degradation of PPARγ, and induced PPARγ transcriptional activity. Using Mesenchymal Stem Cells, we show that Δ^9-THCA is a low adipogenic PPARγ agonist and promotes osteoblastogenesis measured by specific staining and qPCR determination. In docking analysis, we detected that Δ^9-THCA binds both the canonical (Ser289) and the alternative binding sites (L340 and Ser342) in the PPARγ ligand-binding pocket. In addition, we have investigated the effect of Δ^9-THCA in a murine model of metabolic syndrome induced by high fat diet (HFD). Daily administration of Δ^9-THCA (20 mg/kg) for 3-wks induced a significant reduction in fat mass and body weight gain in HFD mice. Δ^9-THCA significantly ameliorated also glucose intolerance and insulin resistance in HFD animals. Moreover, Δ^9-THCA largely prevented liver steatosis, adipogenesis, and macrophage infiltration in fat tissues (Crown-like-structures) of HFD fed mice. Cytokine and Adipokine Proteome Profiler arrays and multiplex analysis demonstrated that Δ^9-THCA has a unique anti-inflammatory profile that correlates with the transcriptomic changes identified in the fat tissue.

In conclusion, our studies document the potent biological activity of Δ^9-THCA as a non-adipogenic PPARγ agonist highlighting its potential to ameliorate metabolic syndrome and inflammation associated to obesity.

VId. Evaluation of novel pharmacogenetic tools for the activation of the Kiss1 neurons located in the arcuate nucleus

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Reproductive function is under the control of a plethora of signals that ensures fertility and, hence, the perpetuation of the species. Kisspeptins, neuropeptides produced by Kiss1 neurons, have emerged recently as one of the most important elements in the control of the reproductive axis; kisspeptin deficiency causes hypogonadotropic hypogonadism and infertility. While much has been learnt in recent years on the physiology of Kiss1 neurons, development of new tools for manipulation of these neurons is crucial to deepen our knowledge about their function and interaction with other reproductive (and metabolic) signals.

The aim of this work was to set-up a protocol for the manipulation of the population of Kiss1 neurons located in the arcuate nucleus (ARC), which is involved in the pulsatile secretion of GnRH/LH and mediates the negative feedback of gonad steroids on gonadotropin secretion. To this purpose, we used virogenetics tools for the expression of the stimulatory DREADD (Designer Receptors Exclusively Activated by Designer Drugs) hM3Dq in the ARC and its activation by the selective ligand clozapine-n-oxide (CNO).

Our results demonstrated that viral injections for delivery of hM3Dq-expressing vectors to the ARC target only a modest fraction of Kiss1 neurons, with some individual variability. Nonetheless, activation of this DREADD by CNO in vivo elicited a significant increase in LH release, which correlated with the number of Kiss1 neurons expressing hM3Dq.

All in all, our results suggest that our protocol for the pharmacogenetic activation of Kiss1 neurons is effective in vivo and may help to study the function of this neuronal population and its implications in different physiological functions. Additional analyses involving higher number of animals and other forms of virogenetic manipulation of Kiss1 neurons are currently in progress in our group to further validate our initial results.

VIe. Growth hormone signals via Stat5b to suppress hepatic glucokinase and de novo lipogenesis

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Congenital hepatocyte-specific loss of GH signaling (knockout of GH receptor [GHR], Jak2 or Stat5a/b) leads to steatosis and predisposes the liver to injury. We have extended these observations to reveal adult-onset loss of the hepatocyte GHR (aHepGHRkd) promotes steatosis, by enhancing *de novo* lipogenesis (DNL). With time aHepGHRkd mice show sustained DNL, associated with hepatocyte ballooning, inflammation and mild fibrosis, all early signs of nonalcoholic steatohepatitis (NASH). In order to see if loss of the GHR would also exacerbate steatosis in response to a diet known to promote NASH (Hffc diet: high-fat, high-fructose, high-cholesterol diet), aHepGHRkd and GHR-intact control mice were fed the Hffc diet for one-month and tissues collected. Liver weight and hepatic triglyceride (TG) content was dramatically increased in aHepGHRkd mice. The increase in TG was associated with increases in fatty acid (FA) indices indicative of DNL. Since aHepGHRkd reduces hepatic phospho- (active) Stat5b, we hypothesized that loss of Stat5b activity is the primary driver of DNL and steatosis. To test this, we generated an adeno-associated viral vector expressing a thyroxin binding globulin promoter (hepatocyte-specific), N-flag tagged, constitutively active Stat5b (AAV8-TBGp-Stat5b^{CA}). Mice with fatty livers, induced by one-month consumption of the Hffc diet, were injected with AAV8-TBGp-Statb^{CA} and 7 days later, hepatic nuclear N-flag tagged Stat5b^{CA} was detected by Western blot and was associated with enhanced IGF1, IGFALS and SOCS2 expression, compared to AAV8-TBGp-Null treated controls, confirming the Stat5b^{CA} was appropriately targeted and active. In addition, hepatic TG content and FA indices of DNL were reduced. Of note, we observed glucokinase expression is elevated in aHepGHRkd mice and suppressed by Stat5bCA. Taken together, these data strongly suggest that Stat5b suppresses hepatic lipid accumulation by reducing glycolysis-driven DNL. It remains to be determine if Stat5b will also protect against NASH development.

VIf. Dietary pattern effect on endothelial dysfunction and vascular homeostasis in patients at risk of cardiovascular events: CORDIOPREV study

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Background: Endothelial dysfunction is an initial step in the development of atherosclerosis. Lifestyle factors, such as diet, influence endothelial function but there are no studies establishing a dietary model that improves endothelial dysfunction in patients at high risk of cardiovascular events.
Objective: We determined whether consumption of a dietary pattern (Mediterranean diet or low-fat diet) improves endothelial dysfunction in coronary heart disease (CHD) patients and whether this improvement was associated with a balance between endothelial injury and repair mechanisms.
Design: In this randomized, single-blind, controlled dietary intervention trial, 1002 CHD patients were included and classified according to brachial artery flow-mediated dilation (FMD) cutoff values: FMD<2%, severe endothelial dysfunction (at high risk of cardiovascular events) and FMD≥2%, non-severe endothelial dysfunction (at lower risk). We evaluated FMD, endothelial damage [endothelial microparticles (EMPs)] and regenerative capacity [endothelial progenitor cells (EPCs)] before and after one year of dietary intervention [Mediterranean diet (35% fat, 22% MUFA and <50% carbohydrates) and a low-fat diet (28% fat, 12% MUFA and >55% carbohydrates)].
Results: Mediterranean diet increased FMD, EPC levels, accompanied by a decrease of activated EMP levels. The low-fat diet did not affect FMD in any group of patients. However, this diet increased EPC levels only in those with non-severe endothelial dysfunction and produced an increase in endothelial damage processes regardless of the severity of endothelial dysfunction.
Conclusions: Our data suggest that a Mediterranean diet, but not a low-fat diet, improves endothelial dysfunction in CHD patients, even in those at high risk of cardiovascular events. These findings highlight the clinical need to identify subgroups of patients at who must be treated more aggressively establishing therapeutic dietary strategies that improve endothelial dysfunction, by a proper balance of vascular homeostasis.

POSTER
Abstracts

POSTER SESSION I
Cancer (Oncology and Oncohematology)

P1. DYRK2 novel regulation mechanism determine its activity via cis-autophosphorylation compromising cell cycle, DNA damage response pathway and carcinogenesis.

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DYRK2 protein kinase is known to have a key role in the regulation of cell processes such as proliferation and cell differentiation, as well as a relevant part in tumour development and/or progression. Despite being considered by the scientific community an "essential protein" for the control of tumourigenesis, the regulatory mechanisms of its activity still remain unknown. In this work, we describe for the first time a new regulation mechanism by autophosphorylation of this kinase. Through in vitro kinase assays and later analysis with mass spectometry, we describe 5 autophosphorilation residues (Thr32, Thr33, Thr82, Ser483, Thr488). Single mutants for each residue show a slightly higher protein stability, also preserving kinase activity intact, as well as the ability of self-phosphorilation and substrate phosphorilation both in vitro and in vivo. Conformational analyses based on X-ray crystalography show the importance of these residues in the native conformation of the enzyme. Through different experimental approaches we demostrate the ability of autophosphorylation in cis and significant differences on the activity of several known substrates, such as c-jun or SIAH2. This has important functional consequences due to the alteration of signalling pathways as relevant as the control of the cell cycle or cell differentiation. By analysing the somatic mutations described in human cancer, we show the existence of mutations with a function-structure similar to those we described in this study. These results help us explain the alterations in cell signalling pathways, as well as the biological significance in the progression of cancer associated to mutations in DYRK2. To conclude, our results demostrate for the first time the existence of a self-regulation mechanism of the activity of this kinase, with a relevant role in the control of tumorigenesis, which could be subjected to a possible pharmacological regulation with a potential clinical use.

P2. Reprogramming the methylome of human cancer cells by expression of a plant DNA demethylase.

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Background: Methylation of cytosine (5-meC) is a stable, but reversible, epigenetic mark that promotes gene silencing. The alteration of DNA methylation patterns is a key factor in several forms of many human diseases, and in particular in most types of cancer, which often show an aberrant methylome. The nature of the enzymatic mechanism(s) responsible for active DNA demethylation in animal cells remains poorly understood. In plants, however, our previous genetic and biochemical studies have revealed that the *Arabidopsis thaliana* DNA glycosylase DME functions as a DNA demethylase that releases 5-meC through a mechanism analogous to base excision repair.
Objetives: To analyze whether expression of DEMETER (DME), a plant enzyme that excises 5-meC from DNA, can revert the abnormal methylation pattern of human cancer cells.
Methods: We obtained stable transfectants in DLD-1 cells expressing wild type or mutant DME protein. Then, we analyzed local and global methylation status of transfected and control cells by qMSP, bisulfite pyrosequencing and HumanMethylation450 BeadChip array, among other techniques. Gene expression levels were measured by qPCR. Additionally, the effect of DME expression on the phenotype of DLD-1 cells was studied by drug resistance assays, colonosphere formation and cancer growth *in vivo* analysis in a mouse xenograft model.
Results: We show that expression of Arabidopsis 5-meC DNA glycosylase DME in DLD-1 demethylates and reactivates hypermethylated silenced loci. Interestingly, DME expression causes genome-wide changes that include both DNA methylation losses and gains, and partially restores the methylation pattern observed in normal tissue. Furthermore, such methylome reprogramming is accompanied by increased sensibility to anti-tumor drugs, decreased ability to form colonospheres, and tumor growth impairment *in vivo*.
Conclusions: The expression of a plant 5-meC DNA glycosylase in human colorectal cancer cells partially reverts their aberrant methylation and alters their tumor phenotype. Plant DNA demethylases, with no counterpart in human cells, may provide new options to study the functional role of DNA methylation in cancer.

P3. Presence and pathophysiological role of the reelin system in glioblastomas

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Reelin-glycoprotein and its functioçnal system (receptors: LRP8 and VLDLR; adaptor-protein DAB1) are essential components for brain-development and to define adult neuronal-plasticity. However, evidences also indicate that some components of the reelin-system could be expressed during brain-tumorigenesis, but the pathophysiological relevance of this finding has not been studied hitherto. Therefore, the aim of this study was to perform a compressive characterization of the reelin-system expression in brain-tumors, and to evaluate its putative role in tumor-progression. Specifically, we analyzed the expression of reelin-system in: 1) glioma tissue-samples obtained from a well-characterized cohort of patients [n=35: low-grade gliomas (LGG; n=4 grade-II and, n=7 grade-III) and glioblastoma multiforme (GBM, grade-IV; n=24); using quantitative-PCR] and; 2) an online brain-tumor dataset containing histological/genetic/molecular/demographic-data of 1018 patient (458 LGG and 564 GBM). Data from our patient's cohort revealed a consistent higher LRP8 expression followed by VLDLR and reelin in gliomas grade-II, -III and -IV, and that the expression of the reelin-system components seems to decrease according to a higher tumor-grade. Remarkably, Kaplan-Meier curves obtained from the online brain-tumor dataset showed that a low reelin, LRP8 and DAB1 levels were associated to a lower survival-rate. Only 7% and 6% of GBM presented mutations in isocitrate-dehydrogenase (IDH) and ATRX, while 81% and 37% of LGG were positive for these mutations, respectively. Moreover, Telomerase-Reverse-Transcriptase (TERT) expression was lost in 56% and 17% of LGG and GBM, receptively. Interestingly, lower levels of reelin, LRP8 and DAB1 were observed in IDH-mutant, while tumors expressing TERT or wildtype-ATRX showed elevated reelin and VLDLR and decreased LRP8 and DAB1 levels. Altogether, this data indicates that the expression levels of some components of the reelin-system are dysregulated in brain-tumors which may be associated to the presence of mutations suggesting that some of these components may be used as novel prognosis biomarkers and therapeutic target in brain-tumors.

P4. Antitumoral effects of splicing inhibitor Pladienolide B in hepatocellular carcinoma cell lines

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Hepato-carcinogenesis is a multistep process involving different genetic alterations that ultimately lead to a malignant transformation of the hepatocyte. The incidence of hepatocellular carcinoma (HCC) is increasing and represents the sixth most common cancer worldwide, often associated with poor prognosis. HCC is one of the most lethal malignancies worldwide because of its aggressiveness and the limited therapeutic options, representing the third most frequent cause of cancer-related death. Although treatment options have improved, no effective chemotherapy exists for the advanced disease. In this scenario, there is emerging evidence that alternative mRNA splicing is dysregulated in many different tumors, including HCC. For that reason, novel drugs capable to modulate the splicing process could represent alternative therapeutic avenues against these tumor pathologies. Hence, our objective was to explore the putative role of the splicing inhibitor, Pladienolide-B, in three different HCC cell-lines with increasing aggressive grade (HepG2, Hep3b and SNU/387) by using a battery of functional in vitro assays. Our results demonstrated that Pladienolide-B is able to significantly reduce the proliferation rate in all HCC cell-lines in a dose-dependent manner. In addition, Pladienolide-B was also able to drastically reduce other functional parameters associated with tumor malignancy in these cell-lines such as migration and formation of colonies and tumorospheres. Moreover, we also determined the expression levels of selected components of the major and minor spliceosomes, splicing factors and splicing variants, using a microfluidic-based qPCR array, in response to Pladienolide-B treatment to demonstrate that key splicing components and variants that have been associated to HCC pathogenesis were dysregulated with Pladienolide-B treatment. Therefore, these results suggest a close relationship between Pladienolide-B treatment and the dysregulation of splicing machinery, which leaded to the reduction of aggressive features of three HCC cell-lines, therefore providing new therapeutic tools for this devastating pathology.

P5. Gut microbiota composition as tool for early diagnosis of colorectal cancer.

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Introduction: Colorectal cancer (CCR) is one of the most prevalent cancers in developed countries. Several studies suggest that the CCR may be related with changes in the gut microbiota.

Objetive: Our study is focused in the development of a screening test for the people in risk, valid and safe, improving the screening prognosis. The main improvement lies in the fact that the proposed method is more specific and sensitive than the current method, fecal occult blood. Our method will be able to distinguish whether fecal occult blood is due to fissures, not related with CCR (which are positive for fecal occult blood, false positive) and is more sensitive (sometimes the polyps do not leak blood).

Materials and Methods: A total of 500 individuals at risk (age > 50 years) from the Junta de Andalucía's screening program will be invited to participate in this study. In our ongoing study we have already included 37 patients. We collected a fecal sample from all the patients positive for the fecal occult blood test, to which a colonoscopy was performed.

Results: We observed that 4 patients (10.81%) presented adenocarcinomas (CRC), 23 patients (62.16%) had adenomatous polyps (premalignant lesion) and 9 patients (24.32%) had no lesion in the results of the colonoscopy. In addition, a patient refused to have a colonoscopy.

Conclusion: Taking into account that from 37 patients analyzed, 4 presented CRC, our results support the idea about the importance of the screening programs in population at risk of CRC. In addition, on the basis of the current method, it is needed to develop a tool for early diagnosis of CRC more specific and safer than the fecal occult blood test, currently used, which may also avoids performing an unnecessary colonoscopy, thus reducing costs and the potential rejection to this invasive test.

P6. Characterization of the KiSS1/KiSS1-R system in pancreatic neuroendocrine tumors and its functional role in tumor pancreatic cell lines

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Pancreatic neuroendocrine tumors (panNETs) are a diverse and heterogeneous group of tumors arising from pancreatic islets. Their rarity and heterogeneity have made very difficult the identification of common molecular signatures and the development of efficient therapeutic approaches. Currently, panNETs molecular pathogenesis remains unknown and no clinical or molecular distinctive features are available to predict their prognostic or therapeutic treatment success. It has recently been suggested that regulatory systems integrated by G-protein coupled receptors could play an important role in the development and/or progression of different endocrine-related tumors. Specifically, some studies have previously reported that the KiSS1/KiSS1-R system is involved in cellular processes such as proliferation, migration, metastasis and angiogenesis in endocrine and non-endocrine pathologies. Therefore, we determined the presence of KiSS1/KiSS1-R system in human panNET tissues (n=46, including both tumor and non-tumor adjacent-regions) and in two NETs cell-lines by quantitative-PCR. We found that KiSS1 expression was elevated while KiSS1-R expression was decreased in panNET tissues compared to non-tumor adjacent-tissues. Interestingly, KiSS1 expression were decreased in functioning panNETs compared to non-functioning tumors suggesting that KiSS1 levels might be associated with tumor functionality. Remarkably, KiSS1 expression appears to be upregulated whereas KiSS1-R expression was significantly reduced in metastatic panNETs compared to non-metastatic pancreatic tumors. Kisspeptin-10 treatment inhibited cellular proliferation and migration in NETs cell-lines. Furthermore, KiSS1-R overexpression reduced while KiSS1-R silencing increased aggressiveness of NET cell-lines in terms of cell proliferation and migration rates. In conclusion, our results provide evidence for the putative pathophysiological role of the KiSS1/KiSS1-R system in panNETs and, suggest that some components of this system might be used as potential diagnosis/prognosis biomarkers and/or therapeutic targets in panNETs.

P7. Enhancement of detection coverage in the untargeted metabolomics analysis of urine

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Urine is characterized by a variable composition considering that this biofluid contains the end-products of many biochemical metabolic pathways. Additionally, urine presents several advantages such as an easy and non-invasive sampling, and the collected volume that is enough from an analytical perspective. For these reasons, urine is one of the most frequently used samples in clinical and nutritional metabolomics studies. The main limitation found in the untargeted analysis of urine is the complexity of its composition, difficult to address by using a unique analytical platform, GC–MS or LC–MS. One of the alternatives available for well-equipped analytical laboratories is the integration of data generated by different analytical platforms (GC–MS, LC–MS and NMR). However, the access to such sophisticated instrumentation is not always viable. Therefore, a current research line in metabolomics analysis is the development of methods with high detection capability, which could be achieved with innovations in the detection step as well as in sample preparation.
The aim of this research was to enhance the detection capability in untargeted metabolomics analysis of urine by LC–MS/MS. Firstly, different MS2 data acquisition methods were tested by using a QTOF mass detector. Particularly, three data-dependent acquisition (DDA) modes, namely, conventional DDA, Gas Phase Fractionation (GPF) and staggered GPF were assayed. The results evidenced that GPF and sGPF allowed improving the acquisition of MS2 information versus conventional DDA, 81.3% and 82.9% of scanned entities with GPF and sGPF versus 55.2% with DDA. In conclusion, GPF and sGPF could lead to a comprehensive analysis of urine, which is of interest considering the promising detection of markers for specific applications such as prostate cancer diagnostic.

P8. A comparative study of the functional effects of somatostatin, neuronostatin and cortistatin in prostate cancer cells.

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Somatostatin (SST), neuronostatin (NST; which arises from SST-gene), cortistatin (CORT) and their receptors [SST/CORT-receptors (sst1-5, sst5TMD4-TMD5), NST-receptor (GPR107)] comprise a pleiotropic hormonal-system involved in the regulation of a wide range of physiological functions. Interestingly, some components of SST/CORT/NST-system, especially SST/CORT-receptors, are expressed in tumor-cells and are associated to antitumor actions in numerous cancer-types (e.g. pituitary/breast/prostate...). However, a comparative, parallel, study of the presence and functional role of SST/CORT/NST has not been reported hitherto in any tumor/cancer-type. Therefore, we aimed to investigate the presence of all SST/NST/CORT-system components and the effect of SST/NST/CORT in prostate-cancer (PCa), one of the cancer pathologies with higher incidence worldwide. Expression levels of these components (quantitative-PCR) and functional actions of SST, NST and CORT (10^{-7}M) on cell-proliferation were analysed in different PCa-derived cell-lines [androgen-dependent (LNCaP) and androgen-independent (22Rv1/PC-3; the most aggressive PCa-type)], and in normal-prostate (NP)-cells (RWPE-1 cell-line and primary cell-cultures). Our results revealed that SST/CORT/NST treatments reduced proliferation in androgen-independent, but not in androgen-dependent PCa-cells. Moreover, SST/CORT/NST treatments did not affect NP-cells viability. Interestingly, sst5 and GPR107 were significantly overexpressed in androgen-independent PCa-cells vs. NP-cells, suggesting that SST/CORT and NST actions might be mainly exerted through these receptors in PCa-cells. Remarkably, CORT was highly expressed in all PCa cell-lines, while SST/NST-transcripts levels were very low or not detected, suggesting that local CORT production might be involved in the antitumor actions of this peptide in PCa-cells. Supporting this notion, we found that CORT silencing (by specific-siRNA) drastically increased the proliferation, and that CORT treatment significantly reduced AKT and JNK, but not ERK, phosphorylation levels in 22Rv1-cells. Altogether, our results revealed that local production of different SST-system components might comprise a relevant regulatory circuit that, in conjunction with circulating SST/NST/CORT, may exert antitumor actions and regulate PCa-cells, which provide novel diagnostic and therapeutic tools for this pathology.

POSTER SESSION I
Chronic and Inflammatory diseases

P9. Our experience on the use of biosimilar infliximab in patients with rheumatoid arthritis and spondiloarthritis in conditions of routine clinical practice

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OBJECTIVE: To determine the effectiveness of biosimilar infliximab (Remsima) in comparison with the original drug (Remicade) in a cohort of patients with spondiloarthritis (SpA) and Rhematoid Arthritis (RA) regarding the effectiveness and the persistence of the drug.

Material and methods

Longitudinal observational ambispective study of 12 months length. There were included 64 patients, 30 with RA and 34 with SpA that had begun treatment with original infliximab (Remicade®) (15 RA/15 SpA) or biosimilar infliximab (Remsima®) (15 RA / 19 SpA) in a query of Rheumatology in conditions of usual clinical practice.

RESULTS: Bearing in mind the basal characteristics, the groups were comparable for age, time of evolution of the illness and basal activity in both groups, except ESR and BASFI in SpA. But there was a greater number of patients naive to biological therapy in the group treated with Remicade in front of Remsima. There were 15 patients in front of 10, respectively, for RA, and 10 versus 18 for SpA (p<0,05). We found that 56 had completed the 12 months of treatment (22 Remsima/34 Remicade). In the case of the patients with SpA, we did not find significant differences in the number of interruptions between both drugs, whereas in the patients with RA 7 subjects had to suspend the treatment with Remsima in front of none in the group with Remicade.

CLINICAL EVOLUTION IN RA					
VARIABLE	DRUG	BASAL	6 MONTHS	12 MONTHS	DIFFERENCES
CRP (MG/L)	REMSIMA	16,03 (17,11)	5,40 (8,44)	4,72 (5,28)	-7,45 (16,47)
	REMICADE	8,55 (7,18)	3,55 (2,59)	4,37 (4,99)	-4,17 (8,58)
ESR (MM/1H)	REMSIMA	25,80 (19,83)	17,92 (15,95)	22,00 (17,16)	2,17 (9,70)
	REMICADE	32,07 (27,18)	18,93 (13,10)	21,80 (14,15)	-10,27 (29,77)
DAS 28	REMSIMA	5,03 (1,48)	2,96 (1,46)	2,61 (0,81)	-2,19 (1,29)
	REMICADE	5,11 (1,09)	2,87 (0,99)	3,29 (1,21)	-1,79 (0,86)
HAQ	REMSIMA	1,49 (0,44)	1,17 (0,54)	1,50 (0,44)	-0,07 (0,16)
	REMICADE	1,35 (0,55)	0,91 (0,66)	1,64 (3,04)	0,73 (3,64)
GLOBAL VAS	REMSIMA	70,00 (20,75)	54,55 (19,16)	48,33 (24,83)	-13,33 (25,03)
	REMICADE	67,00 (14,12)	38,00 (20,60)	40,00 (18,29)	-26,79 (19,08)
INFLAMATED JOINTS	REMSIMA	8,38 (6,33)	3,30 (7,20)	0,17 (0,41)	-6,83 (4,07)
	REMICADE	6,47 (5,21)	1,07 (1,75)	0,87 (1,30)	-5,60 (5,25)
PAINFULL JOINTS	REMSIMA	9,00 (5,24)	5,33 (7,12)	0,83 (1,17)	-7,50 (5,54)
	REMICADE	9,40 (6,66)	1,67 (2,26)	1,53 (1,46)	-7,86 (6,84)

Table 1. Means and standard deviations in basal, 6-months and 1-year treatment characteristics. Differences between means after a year of treatment and the basal ones. No significant differences were found in none of both groups. CRP: C Reaction Protein. ESR: erythrocyte sedimentation rate, DAS 28: Disease Activity Score, HAQ: Health Assessment Questionnaire, VAS: Visual Analogue Scale

CLINICAL EVOLUTION IN SPA					
VARIABLE	DRUG	BASAL	6 MONTHS	12 MONTHS	DIFFERENCES
CRP (MG/L)	REMSIMA	18,34 (33,82)	1,28 (1,63)	1,45 (2,34)	-17,28 (36,75)
	REMICADE	41,55 (55,00)	3,24 (6,39)	3,87 (5,82)	-37,68 (56,48)
ESR (MM/1H)	REMSIMA	24,67 (26,31)1	8,50 (5,83)	10,33 (6,76)	-14,33 (19,64)
	REMICADE	42,06 (27,61)1	10,11 (7,29)	11,22 (11,60)	-31,65 (28,95)
BASDAI	REMSIMA	4,70 (2,16)	2,41 (1,48)	2,54 (1,88)	-2,16 (2,27)
	REMICADE	6,09 (1,57)	2,46 (1,96)	2,51 (1,65)	-3,27 (1,83)
BASFI	REMSIMA	4,16 (2,88)2	2,13 (1,96)	2,75 (2,48)	-1,51 (2,08)
	REMICADE	9,44 (10,93)2	2,41 (2,17)	3,24 (4,95)	-3,45 (2,30)
GLOBAL VAS	REMSIMA	56,15 (28,73)	28,58 (23,36)	25,00 (17,16)	-26,00 (33,40)
	REMICADE	63,22 (28,92)	24,44 (18,86)	29,12 (24,51)	-33,12 (32,00)
MEDICAL VAS	REMSIMA	53,85 (31,24)	27,75 (23,10)	24,00 (16,73)	-4,00 (8,94)
	REMICADE	54,59 (29,59)	19,41 (16,38)	13,33 (10,00)	-37,78 (37,68)
MODIFIED SCHÖBER (CM)	REMSIMA	13,95 (5,80)	12,54 (5,25)	14,25 (1,93)	0,01 (2,37)
	REMICADE	12,88 (2,51)	13,97 (1,53)	13,84 (1,47)	0,91 (2,54)

Table 2. Means and standard deviations in basal, 6-months and 1-year treatment characteristics. Differences between means after a year of treatment and the basal ones. 1: Statiscally significant differences were observed in basal ESG between both groups. 2. Statiscally significant differences were observed in basal BASFI between both groups. BASDAI: Bath Ankylosing Spondylitis Disease Activity Index. BASFI: Bath Ankylosing Spondylitis Functional Index.

DISCUSSION / CONCLUSION

1) Patients with RA and SpA have similar response rates to both treatments

2) However, in our cohort, we observed that the number of patients who abandoned the treatment was higher in the group with Remsima and RA.

These data suggest that longer-term and longer follow-up studies are necessary to determine whether treatment with biosimilar drugs leads to a long-term clinical response to that observed with original drugs, under conditions of routine clinical practice.

P10. Applicability of artificial intelligence in determining risk factors of mortality in hemodialysis patients

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Although there have been advances in treatment of maintenance hemodialysis (HD) patients, mortality rates remain elevated. A large number of studies have identified both traditional and uremia-related risk factors by the *classical* statistical approach. This study analyze data available from a Database, a total of 2038 patients started hemodialysis between the years 1995 and 2015, all of them were included in the study.

Variables collected at the initiation of regular HD included were age, comorbidities (Charlson Index), analytical variables, Body Mass Index (BMI), residual diuresis and type of vascular access (VA) for HD. Analysis was performed to assess the independent effect of the variables on the mortality at 6 months, 1 and 2 years of HD.

COX regression identifies independent variables for death, and it provides a relative risk value: the Hazard ratio. The Random Forest (RF) analysis is different; the entire set of data is separated in many different data subsets in a random manner (without prioritization). Decision trees able to identify variables with a potential to predict mortality are performed.

At 6 months, by RF, the most influential variables were BMI, serum creatinine (Crs) and type of VA (native AV fistula favors outcome). From COX Regression analysis, history of Stroke, followed by VA, and Crs were the most influential variables. At 1 year, the most influential variables by RF were BMI, albumin, diuresis and age. Highest HR by COX were on age, stroke and type of VA. At 2 year, BMI, albumin level, diuresis and age were identified as risk factors by RF. By Cox Age, BMI, stroke and VA had significant predictive value.

We found different variables using different method even if the data analyzed is the same. The variables identified by RF are more appropriate that Cox. In conclusion, RF analysis is an alternative valid method to identify variables and generate models that are useful to predict mortality in HD patients.

P11. Motivational interviewing to increase physical activity in elderly people with hip fracture: a systematic review.

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INTRODUCTION: The motivational interviewing is a technique used to achieve behavioral changes that have been demonstrated its effectiveness in different fields.
OBJETIVE: To determine if motivational interviewing leads to increased physical activity in elderly people with hip fracture.
METHODS. ystematic review. Two electronic databases (MEDLINE and the Cochrane Central Register of Controlled trials) were searched. The keywords were: hip fracture, activity, motiv*, motivational interviewing.
The search strategies were:
- Hip fracture AND activity AND motiv*.
- Motivational interviewing AND activity AND hip fracture.
- Motivational interviewing AND activity.
The search strategy was limited to articles published between 2000 and 2018.
Clinical trials and observational study were included if participants were adults (> 65 years), and used motivational interviewing as the intervention and analysed physical activity.
The Grades of Recommendation, Assessment, Development and Evaluation approach were used to evaluate the quality of the evidence.
RESULTS: Twenty studies were eligible for full review. Only five of them used the motivational interview as motivational intervention without further guided exercise sessions. Two articles were eliminated due to low level of evidence. Among the remaining there was a moderate level of evidence. Only one study related motivational interviewing, physical activity and hip fracture. In the others we find a relationship between motivational interview and physical activity. The duration of the interventions and frequency of data collection varied across studies. Baseline, 6 months and 12 months were the most common time points for data collection. The motivational interviewing had a small effect in increasing physical activity levels relative to comparison groups.
CONCLUSION: The addition of motivational interviewing to usual care may lead to modest improvements in physical activity for older people.

P12. Vitiligo skin molecular fingerprinting shows increases in multiple polar cytokine axes

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Background: Vitiligo is a chronic autoimmune depigmentation disorder affecting up to 152 million people worldwide. It has a profound negative impact on patient quality of life and lacks effective therapeutic options. While the current pathogenic paradigm highlights T_H1/IFN-γ upregulation, limited blood data also suggests possible involvement of other cytokine axes. Objective: To elucidate the skin molecular profile of vitiligo. Methods: Comparing gene expression of 41 mollecules by PCR in lesional (LS) and non-lesional (NL) skin samples from vitiligo (n=16) and control individuals (n=8).VIDA severity score was calculated for every patient. Results: Overall, we found significant upregulation of multiple immune pathways in both LS and NL vitiligo skin versus controls. These included significant increases in T_H1 markers (i.e. IFN-γ, CXCL9, CXCL10, and CCL5; $p<0.01$), but also in key T_H2 cytokines and chemokines (i.e. IL-5, IL-13; $p<0.05$, CCL13, and CCL18; $p<0.01$). Less consistent and significant increases were detected in some T_H17/T_H22 markers (i.e. IL-17A, IL-22, and S100A9; $p<0.05$), mostly in lesional skin only. Key mediators of JAK/STAT signaling (JAK3, STAT1) were significantly upregulated in both LS and NL tissues, as was the general inflammation marker MMP12 ($p<0.05$ for all). Conclusion: Overall, our data expands the current understanding of cytokine pathways in vitiligo skin beyond T_H1 skewing, providing a basis for possible future therapeutic targeting.

P13. Anti-citrullinated peptide antibodies are associated with low bone mineral density in rheumatoid arthritis

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Background: Several studies have related anti-citrullinated peptide antibodies (ACPA) with the presence of bone erosion in rheumatoid arthtitis (RA) patients as they induce the differentiation and activation of osteoclasts. Our main aim is to evaluate the association of ACPA with bone mineral density (BMD) in RA.
Methods: Case-control study of 73 RA patients (2010 EULAR criteria) and a long standing disease of 5 years. Demographic and clinical variables were collected. BMD values using densitometry at the lumbar (CL), hip (CT) and femoral neck (CF) were collected. The presence of low bone mineral density (osteopenia: tscore≤-1) and ACPA levels were compared using logistic regression analysis, adjusting variables related to BMD: age, sex, menopause, body mass index (BMI), habit Smoking, disease duration, daily corticoid doses, methotrexate treatment and inflammatory disease activity (DAS28).
Results: A group of 73 patients were included (14 men) with a mean age of 66,45 ± 10,41 years, mean body mass index 28,48±5,22 kg/m^2, mean long standing disease of 2,28±1,75 years and mean DAS 28 of 3,17±1,18. A total of 29 patients were negative for ACPA compared to 44 patients that were positive for ACPA. Osteopenia in lumbar spine was found in 82.2% of patients 65.8% hip and 75.3% in femoral neck. Logistic regression was performed without finding statistically significant association between osteopenia and inflammatory activity (DAS 28), vitamin D levels and positive rheumatoid factor, adjusted for variables that can modify BMD. ACPA Positive (any titer) were associated with the presence of lumbar spine osteopenia (OR 7.19, 95% CI 1.77-29.17) (p = 0.006), hip (OR 15.17, 95% CI 3.96-58.18) (p = 0.001) and femoral neck (OR 3.76; 95% CI 1.20-11.82) (p = 0.023). In addition, a simple variance analysis (ANOVA) was performed to compare T scores and ACPA levels divided into three categories: ≤25U / mL, 25-300U / mL and> 300U / mL.ACPA group ≤25U / mL differed in mean T score values in lumbar spine, hip and femoral neck. No differences were found between ACPA positive patients with low and high levels for T score values.
Conclusions: ACPA positivity in RA is associated with an increased risk of osteopenia in lumbar spine, hip and femoral neck independently of other variables that may modify bone mineral density. These data suggest that ACPA may play a role in bone remodeling.

P14. The deregulation of the spliceosome components in leukocytes from ankylosing spondylitis patients is related to disease pathogenesis and therapeutic response

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BACKGROUND: Ankylosing Spondylitis (AS) is a chronic inflammatory disease whose etiopathogenesis has not been fully clarified. Splicing is a post-transcriptional process involved in the RNA maduration. Recent studies reveal that a pathological deregulation of the spliceosome is associated to several diseases.

OBJECTIVES:

1) To evaluate the deregulation of spliceosome in AS leukocytes.

2) To analyze the in vivo effects of anti-TNFalfa drugs on the spliceosome components of AS leukocytes.

METHODS: Thirty two AS patients and 29 healthy donors (HDs) were included in a cross-sectional study. Eight patients were selected for a 3-month longitudinal study of anti-TNFalfa response. Disease activity (BASDAI, CRP and ESR), physical function (BASFI), spinal mobility (BASMI), and structural damage (mSASSS) were collected. The expression of 48 spliceosome components of and splicing factors was evaluated in purified leukocytes by Fluidigm methodology; inflammatory marker expression was determined by RT-PCR.

RESULTS: Compared to HDs, a significant deregulation in the expression of splicing factors and spliceosome components was found in lymphocytes, monocytes and neutrophils from AS patients. Interestingly, a specific altered profile of spliceosome members was observed when comparing the three leukocyte subsets analyzed. Correlation studies revealed that inflammatory profile, disease activity and structural damage were associated to alteration of a vast number of spliceosome components in all the leukocytes evaluated. BASFI correlated with the expression of SKIP and U6atac in neutrophils.

Anti-TNFα treatment reversed the altered expression of spliceosome components and splicing factors in PBMCs and neutrophils, a fact associated with reduced disease activity.

CONCLUSIONS:

1) AS patients display a deregulation of the spliceosome components associated to disease function, activity, inflammation and structural damage.

2) Anti-TNFα may partially reverse the altered expression of spliceosome components and splicing factors.

3) Alteration of the spliceosome may provide new biomarkers for disease and therapeutic response in AS. Funded by: JA-PI-0139-2017, ISCIII (RIER RD16/0012/0015).

P15. Characterization of the transcriptomic profile of Antiphospholipid syndrome patients related to their atherothrombotic status. Effects of *in vivo* Ubiquinol supplementation.

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Objectives: 1. To characterize the molecular profile of monocytes as key players in the pathology of Antiphospholipid Syndrome patients (APS). 2. To evaluate the role of antiphospholipid antibodies (aPL) in the regulation of these processes. 3. To investigate the short-term effects of *in vivo* ubiquinol (reduced coenzyme Q10 [Qred]) supplementation.
Methods: Monocytes from peripheral blood of 60 subjects, including 30 APS patients and 30 healthy donors were purified by negative immunomagnetic selection. Microarray studies were performed in an Agilent G4112F platform (Whole Human Genome Microarray 44k). Functional categorization of the altered genes was performed using Ingenuity Pathway Analysis Software (IPA). Most differentially expressed genes were validated by RT-PCR in the whole cohort. Correlation and association studies were performed with clinical and analytical variables. The effects of aPL were evaluated by *in vitro* studies. The short-term effects of *in vivo* Qred supplementation on the monocyte gene profile were further analysed.
Results: Microarray identified 518 altered genes in APS monocytes. Main canonical pathways integrated by these genes were leukocyte adhesion, diapedesis and extravasation signaling, interleukin and cytokine signaling, and oxidative stress. Gene alterations were validated in the whole cohort,demonstrated to be stable along the time, divergent of the gene profile in monocytes from non-autoimmune thrombotic patients, and associated to clinical parameters, including thrombotic recurrences and early atherosclerosis. *In vitro* studies demonstrated the specific modulation of several genes by direct effect of aPLs. *In vivo* Qred supplementation of APS patients significantly improved the monocytes' atherothrombotic gene profile.
Conclusions: 1. Gene expression profile allowed the identification of relevant genes and pathways altered in monocytes of APS patients, associated with the pathogenesis of the disease and modulated, at least partially, by aPLs. 2. We have branded novel and specific mRNAs related to CVD in APS monocytes, further modified by effect of *in vivo* Qred supplementation.

P16. Cardiovascular risk in long-term juvenile idiopathic arthritis.

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Introduction: Juvenile Idiopathic Arthritis (JIA) is one of the more common chronic diseases of childhood that often persists into adulthood and can result in significant long-term morbidity, including physical disability. The long-term risk of cardiovascular disease for individuals with Juvenile Idiopathic Arthritis (JIA) remains uncertain.

Objective: This study aims to determine whether adults with JIA in remission and medium-long duration of the disease have an increased risk of cardiovascular disease.

Methods: This is a cross-sectional study including 25 patients (14 females and 11 males) diagnosed with JIA according to the International League of Associations for Rheumatology criteria (ILAR 2001) were compared to 20 age- and sex-matched controls. Remission was determined by JADAS27<1 and according to Wallace criteria. An extensive clinical analysis including body index mass, lipid profile, HOMA-IR and intra-arterial blood pressure was performed. Intima media thickness of the common carotid artery (CIMT) was measured as a marker of subclinical atherosclerosis. Different proinflammatory cytokines (TNFa, IL1b and IL6), molecules involved in the endothelium dysfunction (VEGF and E-Selectin) and adipokines (resistin and visfatin) were analyzed on serum by ELISA.

Results: Mean duration of the disease was 13.31 ± 1.14 years. Mean age was 27.21 ± 0.68. Time in remission was 3.52±0.84 years. Metabolic comordibities such as obesity and metabolic syndrome were more prevalent in our cohort of JIA patients compared to controls. Levels of cholesterol were significantly elevated in patients. However, HOMA-IR values and intra-arterial pressure were not significant increased in JIA patients. CIMT was higher in JIA patients compared to controls (0.44± 0.009 vs 0.41± 0.017, p=0.078), although it did not reach the statistical significance. Serum levels of cytokines (including TNFa, IL6 and IL1b), adipokines (such as resistin and visfatin), and VEGF were significantly augmented in the cases vs healthy donors. In addition, IMT values significantly correlated with the disease duration (r=0.439, p=0.046) and serum VEGF levels (r=0.498, p= 0.030).

Conclusions: In our cohort of JIA patients the increased CIMT was not associated with inflammatory markers, but disease duration. Although patients were in clinical remission, the serum levels of inflammatory cytokines, adipokines and VEGF were elevated, molecules with a relevant role in the onset and progression of endothelial dysfunction and atherosclerosis. These results might suggest that long-term JIA patients could have higher cardiovascular risk, although they are in sustained remission.

P17. Evolving Nuss Technique. A single center experience.

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Objectives: To review the evolving technique of minimally invasive repair of pectus excavatum (PE) performed at our institution over a 17-year period.
Methods: Retrospective review of all PE patients undergoing surgical repair by the Nuss Procedure from January 2001 to December 2017. Demographic, surgical and postoperative variables were recorded and compared between early era (from 2001 to 2012) and late era (from 2013 to 2017). Groups were defined according to main changes in operative technique (surgical approach, number of stabilizers and chest drains). Non-parametric tests were used for comparisons.
Results: 65 patients (20±7 yrs; 59M/6F) were included. 4 patients had a perceived limitation of exercise ability, 5 presented a progression after a Ravitch procedure, and the remaining 56 underwent surgery for cosmetic reasons. Comparative analysis (early – 30 patients vs. late – 35 patients): Age (21±8 vs 18±5; p=0.15), gender (M/F) (28/2 vs 31/4; p=ns), Haller Index (9.4±9 vs 3.8±1, p=0.07), early complications (10 vs 2, p=0.005; pneumothorax 4 vs 1p=0.13; haemothorax 2 vs 0 p=0.21; bar displacement 3 vs 1, p=0.25, other 2 vs 0, p=0.46); mean bar duration (2.3 vs 2.1 years p=0.8); hospital stay (7±4 vs 4±1 days, p=0.004); cosmetic results (excellent/good/poor) (25/3/2 vs 33/2/0, p=0.23). Neither fatal complications nor PE recurrence after bar removal were recorded.
Conclusions: The Nuss procedure is a safe and effective technique to repair PE deformities. The experience gained over time in our Institution allowed us to lessen the invasiveness and reduce complications with excellent long-term results.

POSTER SESSION I
Infectious and Immunological diseases. Organ transplantation

P18. Lack of hepatitis c uptake in hiv parenteral drug users

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Background: Strategic plans have been developed to eradicate Hepatitis C virus (HCV) worldwide in the next years. Understanding patient factors associated with being untreated for HCV would help in supporting extra efforts in those patients to achieve HCV elimination in the coming years.
Methods: HIV infected patients with active chronic HCV infection included in the HERACLES cohort (NCT02511496) constituted the study population. The main study outcome was receipt of HCV DAAs treatment from May 1, 2015 to May 1, 2017. The population description was divided into patients who were receiving HCV treatment during follow-up and those who were not.
Results: Of the 15,556 HIV patients in care, 3,075 (19.7%) presented with chronic HCV infection and constituted the study population. At the end of the follow-up, 1,957 patients initiated HCV therapy (63.6%). Age lower than 50 years, absence of or minimal liver fibrosis, treatment-naïve patients, HCV genotype 3 infection, people who injected drugs using opioid substitutive therapy (OST-PWIDs), and recent PWIDs were identified as significant independent risk factors associated with low DAA implementation. When a multivariate analysis was performed and only included the PWIDs population, both OST-PWIDs (OR [95% CI] = 0.552 [0.409-0.746]) and recent PWIDs (OR [95% CI] = 0.019 [0.004-0.087]) were identified as independent factors associated with low treatment implementation.
Conclusions: we identified factors, which did not include prioritization of DAAs uptake strategy, that limited the access to HCV therapy. The low treatment uptake in several populations seriously jeopardizes the completion of the HCV elimination in the coming years.

P19. Substitutive growth hormone therapy in smallforgestationalage children according to their diagnosis in reina sofia hospital

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INTRODUCTION: Small for gestational age (SGA) is a well-known indication for growth hormone (GH) therapy. However, it is also known that all SGA children usually reach final height -1SD below the mean. It could be useful to classify these patients into three groups according to small length (SGA_L), small weight (SGA_W) or both at birth (SGA_{W+L}), to find out possible growth evolution differences between them.
OBJECTIVE: To evaluate and compare GH therapy effectiveness in SGA children according to their size at birth.
METHODS: Retrospective descriptive study of SGA children followed until final height.
RESULTS: 87 SGA children (46 boys/41girls) were followed during 13 years. 47.12% (54% boys/46% girls) started GH therapy after meeting specific criteria (height<-2.5 SD). From them, 22% (9/41) were SGA_W, 17% (7/41) SGA_L and 61% (25/41) SGA_{W+L}. SGA_W and SGA_{W+L} were mostly boys (5:4 and 15:10), and SGA_L, girls (5:2). The mean age before starting treatment was 7.62 years old and the mean height was -2.8 SD in SGA_W, -2.9 SD in SGA_L and -3.4 SD in SGA_{W+L}. All of them showed an improvement in height percentiles after the first year of treatment: 0.36SD, 0.68 SD and 0.71 SD, respectively, which was progressively slower in all groups during the 13 years. These evolutions show a gain of height of 1.46SD (SGA_W), 1.47SD (SGA_L) and 1.66SD (SGA_{W+L}) The final adult height was -1.7 SD, -1.43 SD and -1.7 SD, respectively. The three groups reached their target height (0.35 +/- 0.08 SD).
CONCLUSION: Less than half of SGA children in our group required GH therapy. The greatest effectiveness of GH therapy occurred after the first year in all groups but SGA_L group showed the best final adult height, compared with the other two groups.

P20. C3 deposits worsens the prognosis in type III EXTRACAPILLARY glomerulonephritis

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Introduction
Type III extracapillary glomerulonephritis (PEGN) is a common cause of rapidly progressive glomerulonephritis and it is usually associated with circulating anti-neutrophil cytoplasmic antibodies (ANCAs). Recent evidence points to complement activation as an important factor in the pathogenesis of PEGN. The aim of the present study was to assess the value of C3 deposits in the prognosis of PEGN.
Methods
All patients diagnosed of PEGN from 1995 to 2015 (n = 72) were included in this study. Progression of renal disease in patients with positive staining for C3 by immunofluorescence was compared with those with negative staining. Mean follow up was 73 months. Progression to end-stage renal disease in relation to clinical and histological variables was analyzed.
Results
Positive staining for C3 was observed in 22 out of the 72 patients (30.5%). At the time of diagnosis, patients with C3 deposits had higher serum creatinine concentration than those without C3 staining (5.00 vs. 3.85 mg/dl, P = 0.050). Renal survival at 10 years was 36.9% in patients with positive C3 staining vs. 64.4% in patients with negative staining (P = 0.005). Mortality at 10 years was higher in patients with C3 deposits than in patients without deposits (77 vs. 49.3%).
Conclusions
Thus, our study shows that PEGN with deposits of C3 is associated with worse renal prognosis and greater mortality. These results would support the hypothesis that activation of the alternative pathway complement may play an important role in the generation of renal injury associated with PEGN.

P21. The nosocomial infections in patients with severe trauma in Intensive Care Unit

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Introduction: Nosocomial infections are the most frequent adverse event and one of the reasons in prolonged stays in intensive care units (ICU). In addition to nosocomial infections, the quality of the care provided determine the prognosis of patients with severe trauma. The aim of our study is to know and analyze the factors related to the development of nosocomial infections in an ICU of a tertiary hospital in southern Spain. Methods: Retrospective longitudinal study with two observations (admission and discharge) performed in an ICU of a third level hospital. Clinical records of people admitted to this unit and coded as CIE 800-959.9 between 2012 and 2016 were analyzed. Using binomial logistic regression analysis, factors associated with the development of nosocomial infection. Results: There were 375 records, with a greater number of men (78.1%) and with an average age of 46.63 ± 18.2 years. 9.2% acquired a nosocomial infection during the stay. The factors associated with the development of infection were: the number of days connected to mechanical ventilation (OR 1.12 [95% CI: 1.03-1.23]) and the number of days in the ICU (OR 1.08 [95% CI: 1.02-1.14]). Conclusion: Nosocomial infections in patients with severe trauma admitted to the ICU are mainly associated with the management of invasive techniques. A multidisciplinary approach is needed, focused on the review of action and care plans.

P22. Review of determining factors of the hemodynamics and dysfunction of the criopreserved pulmonary graftes implanted from ross surgery

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The Ross procedure is an alternative to aortic valve replacement with mechanical valves or pericardial or xenograft bioprostheses. This would involve the replacement of the aortic valve by a pulmonary valve autograft and a substitution of the pulmonary valve with a cryopreserved cadaver homograft.
Regarding complications of aortic autograft and pulmonary homograft, a long-term risk of requiring a reoperation of 20% or more has been described. Regarding the frequency of reinterventions exclusively of the homograft, it has been described between 3% -13% at 5 years and between 7% -21% at 12 years; while regarding the hemodynamics at rest and with maximum exercise, there may be a moderately high gradient across the homograft at the position of the pulmonary valve.
In a long-term follow-up study with 210 homografts, it was estimated that approximately 25% of all of them experienced a structural deterioration of the valve at 12 years. The structural deterioration was mainly translated in the valvular insufficiency and with less frequency in the stenosis. On the other hand, the young age of the recipient appears as the main determinant of reoperation.
In another study with 20-year results, out of 202 patients, 25 of them developed pulmonary homograft dysfunction, but only 8 were reoperated. In another recent study (2018) of follow-up on 100 Ross procedures in the pediatric population, most of the reoperations were related to the right ventricular outflow tract, which can be attributed in part to the lack of growth.
Finally, in a comparative study between decellularized pulmonary homografts versus cryopreserved homografts, a reduced rate of reoperation was observed in the case of the former compared to the latter.
After this review it is clear that there is still much to investigate to clarify its benefits and disadvantages about patients in the future.

P23. Risk of transmission of hepatitis e virus through liver graft in spain

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Prevalence and incidence of Hepatitis E virus (HEV) infection in liver recipient transplant patients have been reported. Nevertheless, there are no data about the prevalence of occult HEV infection in deceased liver donors and its risk of transmission.

The objective of our study was to evaluate the prevalence of HEV infection in liver donors and recipients. Retrospective and cross-sectional analysis of all liver allograft recipients transplanted in the period between 2012 and 2016 whose liver tissue samples were available for its HEV analysis by RT-PCR. Formalin-fixed liver tissue samples analyzed were native explant livers (recipients) and the first available liver allograft biopsy before revascularization (donors). A total of 210 tissue samples from 105 liver recipients (native explants) and 105 donors (liver allograft) were included in the study. HEV RNA was not detected in any of the explant tissue analyzed, meaning that the prevalence of HEV infection was 0%. In the liver graft tissue, one sample was HEV RNA-positive. The prevalence of HEV infection in the liver allografts was 0.95% (95% CI: 0%-5.7%). In conclusion, our study reports the prevalence of HEV infection in both liver organ donors and recipients in Spain, suggesting a potential risk of transmission through this route.

POSTER SESSION I
Active aging and Fragility

P24. EXERCISE IS A GENTLEMAN: LACK OF GENDER DIFFERENCES FOLLOWING A STRUCTURED PAIN-FREE, HOME-BASED PROGRAM FOR CLAUDICATION

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Background: Peripheral arterial disease (PAD) is a common cardiovascular pathology affecting mobility with high prevalence in elderly.
Supervised exercise therapy is a recommended for claudication, however this treatment was found to be less effective in women with PAD following traditional programs. This study retrospectively investigates whether gender differences in functional outcomes are also observable following a structured pain-free home-based exercise program for PAD patients.
Methods: Patients with PAD and claudication enrolled from 2003 to 2016 in a structured home-based program were studied. The program, prescribed at the hospital, was based on two daily 10-minute pain-free walking sessions at a progressively increasing speed. The outcome measures, assessed at baseline and at discharge, were the walking speed at symptoms (PTS) and maximal (Smax) during a treadmill test and the pain-free (PFWD) and total distance walked in six minutes (6MWD). The ankle-brachial index (ABI), program duration and patients' adherence were determined.
Results: A total of 1011 patients (women, n=264; 26%) were enrolled. At baseline, compared to men, women exhibited similar ABI values but lower PTS and PFWD values ($p<0.001$). At discharge, a superimposable number of visits attended, sessions completed and score of adherence was observed in the two groups. Similar improvements were also observed for PTS (0.8±0.8 kmh-1 each), Smax (0.4±0.5 kmh-1 each), PFWD (women: 95±100; men 86±104), 6MWD (women: 32±65; men: 35±58), and ABI (women: 0.07±0.12; men: 0.06±0.11) without between-group differences.
Conclusion: A personalized structured program performed inside the home, which required an average of 16 minutes per day of pain-free walking and of 7 visits at hospital in a year, was equally attended and effective in both women and men. Programs favoring adherence and functional outcomes in women should be tested in prospective studies.

P25. Effect of over-expression of CYB5R3 and caloric restriction on apoptotic signaling in skeletal muscle

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Aging is the time-dependent progressive decline in function with decreased fertility and increased susceptibility of the organism to endogenous and external threats. Nowadays, there is a strong interest in discovering enzymes which allow a healthy aging. NADH-cytochrome b_5 reductase-3 (NADH:ferricytochrome b_5 oxidoreductase, EC1.6.2.2, CYB5R3) is a flavoprotein that catalyzes electron transfer from NADH to cytochrome b_5 or to alternative electron acceptors as plasma membrane coenzyme Q and several exogenous compounds. Previous reports have documented that CYB5R3 is upregulated under caloric restriction (CR), the best defined non-genetic intervention that increases maximum lifespan and improves helthspan. Thus, benefits of this intervention could be mediated, at least to some extent, by CYB5R3 increase. In accordance, mice over-expressing CYB5R3 display a moderately extended lonvegity and exhibit protection against induced cancer, improvement of mitochondrial function and decreased oxidative damage. Given the relationship between aging and cellular apoptosis, we have hypothesized that maximization of mitochondrial efficiency in CYB5R3-transgenic mice may lead to less generation of oxidant species and decreased apoptotic signaling with a better mitochondrial preservation with aging. In this work, we have studied how apoptotic signaling is affected in skeletal muscle (as a model of postmitotic tissue which is one of the major contributors to whole animal energy expenditure) from 7-mo. old wild-type and CYB5R3-transgenic mice fed for 4 mo. either *ad libitum* or under CR (40% reduction in calorie intake). Our results show alterations in the expression levels of some proteins playing important roles in the apoptotic cascade by this genetic and nutritional intervention.

P26. Age-related parameters and their implication in gut microbiota: findings from the CORDIOPREV study.

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Background: Previous studies showed differences in gut microbiota composition between young and elderly people, but there is not enough evidence regarding the gut microbiota composition and its relation to age related parameters.
Objective Our aim was to determine the composition of the gut microbiota in different age groups and to study the relationship between the composition of the gut microbiota and age-related biomarkers such as relative telomere length (RTL) and oxidative stress in patients with established cardiovarscular disease.
Subjects and Methods: The current study was conducted within the framework of the CORDIOPREV study (NCT00924937). Patients were classified by age and their RTL was measured by real time PCR. Differences in the bacterial community structure were analyzed by 16S sequencing from fecal samples. We also investigated oxidative stress biomarkers.
Results: We observed a significantly higher abundance of the *Enterobacteriales* order (p=0.001; Q=0.007) and *Enterobacteriacea* family, (p=0.001; Q=0.012) in patients between 68-80 years old, compared to the other groups. Furthermore, in this subgroup of patients we observed a lower abundance of *Clostridiaceae* family (p=0.001; Q=0.012) and following genus: *Clostridium* (p<0.001; Q<0.001), *SMB53* (p<0.001; Q<0.001), *Megasphaera* (p=0.001; Q=0.018) and an unidentified genus from *Veillonaceae* family (p=0.002; Q=0.018). We also observed a negative correlation of de glutathion with *Enterobacteriales* order (r^2 = -0.131; p = 0.031) and *Enterobacteriacea* family (r^2 = -0.131; p = 0.031). Moreover, we observed a negative correlation between nitric oxide level and the relative abundance of *Clostridiaceae* (r^2 = -0.145; p = 0.013) and *Clostridium* (r^2 = -0.111; p = 0.039).
Conclusion: Our results suggest that there is a close relationship between the gut microbiota compositions and ageing, moreover, one of the mechanisms involved in it might be oxidative stress modulation. These findings may help the understanding of gut microbiota shaping as a tool to delay ageing or to drive a healthier ageing.

P27. The severity of peripheral arterial disease is not a barrier to exercise therapy in elderly patients with claudication: adherence, functional and clinical outcomes in a cohort of patients enrolled in a home-based pain-free program

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Background: Supervised exercise is recommended for patients with peripheral arterial disease (PAD) and claudication, however PAD severity may limit patients' eligibility and adherence to high-intensity programs. This retrospective observational cohort study evaluates the outcomes of patients with severe PAD enrolled in a pain-free home-based program.
Methods: The program, prescribed during few visits at hospital, is executed at home at symptom-free walking speed. Ankle-brachial index (ABI), pain threshold speed (PTS) and maximal speed (Smax) by an incremental treadmill test were re-evaluated at discharge, when adherence was calculated (score 1-4). The number and date of surgical PAD-related procedures and mortality for a 6-year period were collected from the regional health-service database.
Results: From 826 PAD subjects (606 males; 71±9 years) enrolled between 2006 and 2014, patients with ABI value ≥0.90 were excluded. The study population included 696 patients, 190 with ABI ≤0.50 (SevPAD, 27%) and 506 with ABI 0.51-0.90 (ModPAD, 73%). At baseline SevPAD also differed from ModPAD for lower exercise capacity (PTS: 2.4±0.9 vs. 2.9±1.1 km/h; Smax: 3.0±1.0 vs. 3.5±1.2 km/h; p <0.001).
At discharge compared to ModPAD, SevPAD showed superimposable adherence (3.1/4), higher ABI increase (0.11±0.11 vs 0.04±0.11; p<0.001), comparable functional improvement (PTS: 0.7±0.7 vs. 0.8±0.8 km/h; Smax:0.4±0.7 vs. 0.5±0.7 km/h; p=0.045) but higher rate of peripheral revascularizations and deaths (22% vs 10% and 34% vs 15% respectively p<0.001) at 6-year follow-up. Interestingly, SevPAD at higher vs. lower adherence score (≥3: n=151; <3: n=39), showed a 2-fold higher functional improvement (PTS, Smax p <0.001) at discharge and a lower rate of peripheral interventions and deaths (21 vs 26% p=n.s.; 31 vs 46% p=0.07) at follow-up.
Conclusion: A pain-free home-based exercise program was equally feasible and effective independently from PAD severity. Among severe PAD patients, exposed to worst clinical outcomes, a high program adherence favored better functional and long-term outcomes.

P28. Influence of nursing professional training over work engagement and health in nurses of a public hospital in Spain.

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The quality of cares provided by the nursing staff is determined by different variables that should be analyzed to increase patient security. Among them, work engagement (WE) and the level of education in nurses are especially relevant, since they are directly related to patient mortality. Additionally, there is an important relationship between increased psychological distress and insufficient training in nurses. Therefore, it is necessary to study the relationship among the levels of training and education, WE and health in the nursing staff. The main goal of the present research was to describe and analyze these relationships in the nursing staff from a Spanish hospital. WE was evaluated through the UWES-17 (Utrecht Work Engagement Scale) construct. Similarly, general health was measured using the General Health Questionnaire GHQ-28. We also analyzed several variables related to education and training: continuous training in methodological and clinical disciplines, postgraduate studies and the specialization or profile acquired during work experience. For this task, we designed a quantitative, descriptive, cross-sectional, correlational and comparative study. For data collection, an online survey was designed. The survey was completed by 392 nurses. Data were analyzed using IBM SPSS V.23 software. Data distribution and scales reliability were evaluated. Besides, correlational and comparative analyses among the variables were performed. Our findings show a negative correlation among WE and GHQ-28 subscales. We also found statistically significant differences in health levels based on the specialty or profile. We also found that continuous training in the nursing staff influenced the level of WE. Thus, improving continuous formation could increase the levels of WE in nurses. Institutions should consider these issues in order to prevent health problems in the nursing staff and increase the quality of cares provided to patients.

POSTER SESSION I
Nutrition, Endocrine and metabolic diseases

P29. Defining the role of the adipose tissue extracellular matrix in obesity and metabolic disease

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In obesity, the extracellular matrix (ECM) of the adipose tissue undergoes dysregulated remodelling leading to fibrosis, a major pathogenic mechanism linking obesity to metabolic disease. The ECM is a highly dynamic structure essential in maintaining adipocyte differentiation, function and survival. It comprises multiple molecules, including various types of collagens and proteoglycans, which are secreted by resident cells. Previous proteomic studies from our group revealed increased levels of the proteoglycan, lumican, in the subcutaneous adipose tissue of insulin resistant *vs*. normoglycemic obese individuals. However, the role of lumican in ECM architecture and organization and its contribution to the development of metabolic disease is still unknown. Herein, we aimed at analysing the interaction between the extracellular environment and the adipocytes through the development of a three-dimensional culture system to mimic obesity-associated conditions as well as to investigate the relevance of lumican in adipocyte pathophysiology. 3T3-L1 adipocytes were cultured in collagen I matrices, with or without lumican. Lipid droplet staining (Nile Red) was used to analyse adipogenesis, whilst ultrastructural and dynamic characterization of the collagen matrices was achieved using scanning electron microscopy and physical tests. We also studied the gene/protein expression of cell stress markers. We demonstrated that lumican has an inhibitory, dose-dependent effect on adipogenesis of 3T3-L1 cells, which exhibited reduced lipid droplets as well as signs of both oxidative and endoplasmic reticulum stress and impaired adiponectin production. These effects resulted from both a direct action of this proteoglycan on adipocytes and on the organisation of collagen fibres. In all, these observations suggest that the pathophysiological response of adipocytes depends not only on the increased collagen deposition occurring in obesity but also to changes on extracellular molecules responsible of ECM remodelling and the transduction of environmental cues to the adipocytes.

P30. A microbiota pattern predictive for Type 2 Diabetes Development: from the CORIDOPREV study.

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Background: During the last decade the prevalence of type 2 diabetes mellitus (T2DM) has been continuously on the rise and it has been estimated that the current number of T2DM patients worldwide will double in the next two decades. Therefore, it is essential an early and more effective identification of individuals at high risk for developing T2DM. Recent evidences have come out suggesting the role of the gut microbiota in the T2DM pathogenesis. Based on this, we aimed to investigate whether the gut microbiota composition may be used as an effective biomarker to predict T2DM development.
Materials and Methods: This work was conducted within the framework of the CORDIOPREV study. We included the 462 non-T2DM patients at the beginning of the study, according to the ADA diagnostic criteria, 107 of which developed T2DM during 5 years of follow-up. We analyzed the gut microbiota composition by 16S ribosomal RNA gene (V3 and V4 region) sequencing with the Illumina platform and QIIME software. We used Random Forest algorithm to build predictive models of the T2DM development. Multivariate ROC curve analysis was conducted based on the performance of the models.
Results: Our microbiota-based predictive model showed a greater predictive value (AUC=0.952, sensitivity=0.916, specificity=0.818, accuracy=0.893 and kappa coefficient=0.712) than the current methods based in clinical parameters such as FINDRISC and ADA score (AUC=0.590, sensitivity=0.833, specificity=0.181, accuracy=0.680 and kappa coefficient=0.016 and AUC=0.552, sensitivity=0.638, specificity=0.409, accuracy=0.585 and kappa coefficient=0.039, respectively). Moreover, our microbiota-based model also yielded greater predictive value than the model built using insulin sensitivity indexes derived from oral glucose tolerance test (AUC=0.582, sensitivity=0.701, specificity=0.421, accuracy=0.631 and kappa coefficient=0.111).
Conclusion: Our results suggest the potential use of gut microbiota–based models in T2DM development.

P31. Predictive value of the expression of splicing machinery components in patients at high-risk of type 2 diabetes development: modulation by dietary intervention

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Development of type-2 diabetes (T2D) is critically affected by the loss of phenotypic flexibility. There is emerging evidence suggesting that, under adverse metabolic conditions, alternative mRNA splicing is markedly dysregulated at different levels. For this reason, we hypothesized that such dysregulation could contribute to loss of phenotypic flexibility. Consequently, we aimed to explore whether changes in the splicing machinery in peripheral blood mononuclear cells (PBMCs) may serve as early indicator of T2D development, and if dietary intervention could modulate the expression of these components to reduce the risk of T2D. Thus, the expression pattern of selected components of the major/minor spliceosomes (n=13/4), and splicing factors (SFs; n=28) was determined in PBMCs, isolated from basal and 4h postprandial blood, from non-T2D patients with high-risk to develop T2D (individuals with cardiovascular event included in the CORDIOPREV study). Specifically, 107 patients developed T2D during 5 years of follow-up (incident-T2D) and 108 non-T2D patients were randomly selected as controls. PBMCs of incident-T2DM patients exhibited lower levels of certain spliceosome components and SFs compared to non-T2D controls at the inclusion of the study, which were significantly associated to the risk of T2D-development. In addition, changes in spliceosome components and SFs also exhibited predictive value for T2D-development (AUC>0.95). Results also revealed that the expression of a reduced number of spliceosome components and SFs was influenced by diet in a different manner in incicent-T2D and non-T2D subjects, as several spliceosome components showed an alteration in their expression levels in incident-T2D patients under the different diet conditions. Interestingly, changes were most remarkable during the post-prandial phase and associated to relevant clinical parameters. Altogether, these data reveal the existence of pre-T2D development-associated spliceosome alterations that could be modulated by the diet, suggesting that these changes might help to predict the development of T2D in high-risk patients.

P32. Potential effects of ketoconazole on ACTH-producing and non- ACTH-producing neuroendocrine tumors

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Prolonged hypercortisolism remission after treatment with steroidogenesis inhibitors has been described in patients with ectopic adrenocorticotropic hormone (ACTH) syndrome and some studies suggest an antiproliferative and apoptotic effect of ketoconazole in human cancer cells. Based on this, we explored the putative effect of ketoconazole on ACTH-producing and non-ACTH producing neuroendocrine tumor (NET) cell lines and its combination with somatostatin analogs.
Methods: Cultures of human ectopic ACTH-producing small cell lung carcinoma (DMS-79) and BON-1 pancreatic NET cells were used. Total cell number, apoptosis, cell cycle, chromogranin A (CgA)/proopiomelanocortin (POMC), somatostatin receptor subtype (sst) expression by qRT-PCR, as well as serotonin-, CgA- and ACTH secretion were assesed. Ketoconazole was evaluated alone and in combination with octreotide and pasireotide.
Results: In both cell lines, ketoconazole significantly suppressed the cell growth in a dose- and time-dependent manner. The effect in DMS-79 was predominantly cytotoxic, while in BON-1 pro-apoptotic. Ketoconazole induced an increase in G0/G1 phase in both cell lines and G2/M arrest in BON-1 cells. Serotonin secretion in BON-1 was inhibited by pasireotide, but not with octreotide or ketoconazole, in agreement with a high sst5 and low sst2 mRNA expression in this cell line. None of the compounds alone significantly altered the secretion of CgA, ACTH or the mRNA expression of CgA and POMC.
Conclusions: These results suggest a potential direct inhibitory effect of ketoconazole on cell proliferation, apoptosis and cell cycle in ACTH- and non-ACTH producing NET cells. A non-previously described effect of pasireotide on serotonin secretion was demonstrated.

P33. Microbial metabolites as determinant factor for type 2 diabetes mellitus development: from the CORDIOPREV study

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Introduction: Gut microbiota, which acts collectively as a fully integrated organ in the host metabolism, and their associated-metabolites can be shaped by long-term dietary interventions and influence the type 2 diabetes mellitus (T2DM) progression. Taking into account that gut microbiota encode for around 150-fold more genes that human genome, it is thought that some of a high number of metabolites that the intestinal microbiota synthesizes may have biological activity and therefore modulate physiological processes of the guest organism.
Objective: We aimed to evaluate the potential role of microbial metabolites in the development of type 2 diabetes mellitus.
Materials and Methods: The current work was conducted within the framework of the CORDIOPREV study. From a total of 50 patients (men), which had not a diabetes diagnosis at the beginning of the study, 25 patients developed T2DM and 25 presented no diabetes criteria during the follow-up period. Plasma samples were obtained at baseline and after 3 years of follow-up, and were analysed by Metabolon Company.
Results: We observed different changes in the metabolite profile between groups. In fact, we found that one metabolite related to tyrosine metabolism, one related to benzoate metabolism and two metabolites related to tryptophan metabolism decreased in T2DM-incident group compared to non-T2DM group after 3 years of follow-up ($p=0.036$; $p=0.009$; $p=0.020$; and $p=0.048$, respectively). By contrast, we observed an increase in one metabolite related to benzoate metabolism ($p=0.044$) and another metabolite related to secondary bile acid metabolism ($p=0.043$) in T2DM-incident group compared to non-T2DM group after 3 years of follow-up.
Conclusion: Our results suggest a specific role of several metabolites associated to gut microbiota in the T2DM development and progression. Moreover, our results are in line with previously described about the involvement of tryptophan and tyrosine-related metabolites in the development of T2DM.

P34. Relation between metabolic risk biomarkers and the physical activity level and sedentary in growing stage

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Sedentarism has been associated with development of obesity, but the link with the principal features of metabolic syndrome in children is not sufficiently researched.
The aim was to evaluate the possible relation between sedentarism and physical activity (PA) and the metabolic risk in children.
Methods
633 (4 to 14 years) children from different national Paediatric centers were selected. Waist circumference (WC), fat mass (%), blood pressure, insulin, glucose, homeostasis model assessment (HOMA), and lipid profile were analyzed to evaluate the metabolic risk. The PA was evaluated by accelerometers. An analysis of correlations was carried out to evaluate the associations between the different studied variables.
Results. Including all the groups as together, negative associations between both moderate and vigorous-PA and the most of variables studied, and positive for HDLc, were found. Insulin resistance biomarkers (glucose, insulin, HOMA), showed a positive relation with sedentary activity and negative with light-PA.
When the sample was studied dividing by the pubertal status, a negative relation between all levels of PA and the insulin resistance biomarkers, fat mass, triglycerides (TAG) and the apolipoprotein B were found in prepubertal children. Also, a positive relation between vigorous-PA and HDL-cholesterol, and sedentarism with insulin resistance markers were shown. However, fat mass, diastolic blood pressure, TAG and ApoB were more associated to vigorous-PA at pubertal stage.
Finally, in the group classified by BMI (normal-weight, overweight and obesity), negative relations between PA levels respect to insulin resistance were found in the three levels at prepubertal stage. However, the TAG and ApoB kept the main and strong positive association in the prepubertal obese group.
Conclusion. A sedentary lifestyle seems to be in favor to develop a metabolic risk. However, this risk might avoid or reduce with physical activity, mainly with moderate and vigorous intensities already from a prepuberal stage.

P35. Macrophage polarization in response to obesogenic stimuli

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Obesity and chronic low-grade inflammation are linked to the development of insulin resistance and metabolic disease. Pathological adipose tissue expansion concurs with immune cell infiltration, macrophage activation and inflammation, which trigger cellular stress responses that alter the lipid storage and mobilization capacity and ultimately affect adipocyte environment. Whereas macrophages in lean humans make up around 5% of the cells in the adipose tissue, during obesity they constitute up to 50% of all adipose tissue cells. Macrophages can acquire different phenotypes in response to physiological and pathological conditions. Thus, they can be polarized toward a classical, pro-inflammatory activity M1 phenotype or to an alternative M2 phenotype. In addition, an alternative pathway of macrophage activation, the so-called, metabolic activation, has been proposed to occur in the obese adipose tissue in order to buffer lipid spillover from. Nevertheless, the influence of obesogenic stimuli on macrophage polarization is not fully understood. To address this, we have characterized the phenotype of THP1 macrophages in response to two major hallmarks of obesity, fibrosis and lipid overload. To this end, we have developed collagen I matrices which we proved to mimic the fibrotic environment occurring in obesity. We also explored the effects of the saturated fatty acid, palmitate, on macrophage activation. Our RT-qPCR results show alterations in the expression profile of cytokines in macrophages cultured in a fibrotic extracellular matrix, which mainly exacerbates the pro-inflammatory M1 phenotype. In addition, confocal studies showed that M1, rather than M2 macrophages, accumulate lipids in response to lipid overload, leading to metabolic activated macrophages. Our observations suggest that these obesogenic insults lead to an imbalance in the macrophage population, which could be a key factor in the alteration of adipose tissue homeostasis leading to metabolic disease in obesity.

P36. Non-invasive method for the early detection of metabolic syndrome in the pediatric population

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The Metabolic Syndrome (MetS) occurs in 3.3% of the paediatric population but 11.9% in overweight children and 29.2% in those obese. To date, there is no consensus on a MetS definition for children and adolescents. The early diagnosis of MetS requires a long timeframe and is costly, as each parameter of MetS must be investigated. A good screening test should be both highly predictive and easy to perform and interpret.
Objective: The aim of this study was to assess the diagnostic value of a new non-invasive method for the early detection of metabolic syndrome in the paediatric population.
Methods: We performed a cross-sectional study and a diagnostic test accuracy study using a reference population of children and adolescents aged 6 to 16 in a local population in the South of Spain. The anthropometric variables analysed were: weight, height, body mass index, waist circumference, waist-to-height ratio and blood pressure.
The prevalence of MetS was determined according to the following children guidelines of MetS definition: NCEP-ATPIII, IDF, Cook, and Ferranti criteria. To measure the accuracy of the diagnostic tests, the safety and validity indexes (sensitivity, specificity, negative and positive predictive values, positive and negative likelihood ratios, Youden index and diagnostic validity) were determined. The level of statistical significance was set at an alpha error of less than 5% for all statistical tests.
Results: The Youden index was 0.82 (0.67 -.97), the Sensitivity of 92.3% (74% -100%), Specificity 89.2% (85.1% -93.3%), PPV 31.6% (15.5% -47.7%), NPV 99.5% (98.4% -100%), LHR + 8.6 (5.7-12.7) and LHR -0.09 (0.01-0.57).
Conclusion: This method reduces the use of blood tests for those cases in which confirmation is required. It is a versatile, economic and easily measurable method in any healthcare setting.

P37. Identification of miRNAs as biomarkers for the prediction of atherosclerosis development in patients with cardiovascular disease

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Background: Cardiovascular diseases are the primary cause of death worldwide. The common base of these diseases is atherosclerosis, a process characterized by the thickening of the carotid intima-media. Previous studies have demonstrated that miRNAs can be used as biomarkers of diverse diseases. Our aim was to identify miRNAs as potential biomarkers to predict the development of atherosclerosis, evaluated by the progression or regression of the carotid intima-media thickness, in patients with established cardiovascular disease.
Materials and Methods: From the CORDIOPREV study, we selected a subpopulation of 120 patients with the most extreme progression and 120 patients with the most extreme regression of the carotid intima-media thickness after 5 years of follow-up. Carotid intima-media thickness was measured bilaterally with high-resolution B-mode Doppler echography. Clinical parameters such as triglycerides, low-density lipoprotein, high-density lipoprotein, apolipoproteins A and B, fasting insulin, fasting glucose, and C-reactive protein were measured at baseline. The baseline intracellular levels of 28 miRNAs from peripheral blood mononuclear cells were determined through the OpenArray platform. Binary logistic regression and receiver operating characteristic analyses were carried out to evaluate the predictive potential of our miRNAs set.
Results: A model using only clinical parameters resulted in AUC of 0.581 for the prediction of atherosclerosis development. A model using only 17 miRNAs showed AUC of 0.793. When these miRNAs were used in addition to the clinical parameters, discriminative capacity was greatly improved (AUC= 0.829). Finally, a selection of only 7 miRNAs, which showed significance ($p < 0.05$) in the logistic regression, added to the model with clinical parameters resulted in AUC of 0.801.
Conclusion: Our results show that the addition of a set of 7 miRNAs measured in peripheral blood mononuclear cells, could improve the predictive potential of the clinical parameters used to evaluate atherosclerosis development in patients with established cardiovascular disease.

SESSION II
Cancer (Oncology and Oncohematology)

P38. The expression of splicing machinery components is dysregulated in human craniopharyngiomas

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Craniopharyngiomas are a relatively rare, epithelial tumor that are thought to be derived from remnants of the Rathke-Pouch, an embryological structure that also give rise to the anterior-pituitary. In fact, pituitary-adenomas and craniopharyngiomas are similar in some aspects: both are histologically benign, slow-growing intracranial tumors, and tend to cause similar symptoms and signs (i.e. headache/progressive visual loss/endocrine problems...). Craniopharyngiomas occur most commonly in childhood and adolescence and in later adult-life after age 50 years and, are usually not discovered until they are quite large when associate to severe comorbidities related to mass-effect on important structures (e.g. pituitary/optic nerves or chiasm/intracranial arteries...). The initial treatment for craniopharyngiomas is usually surgery but they typically cannot be completely removed, and their recurrence rates are unfortunately high. Therefore, identification of new molecular markers to better define craniopharyngiomas deem necessary to provide clues for novel therapeutic targets. In this context, there is emerging evidence suggesting that alternative splicing is markedly dysregulated in tumor-pathologies at different levels. Therefore, our objective was to determine whether the expression pattern of splicing machinery components was altered in human craniopharyngiomas. To that end, the expression levels of selected components of the major/minor (n=13/4) spliceosomes, and splicing-factors (SFs; n=28) was determined in human craniopharyngiomas tissues collected [retrospective and prospective (1995-2017 period; Cordoba and Seville Hospitals)] from primary and recurrent surgeries of 36 patients, as well as in normal-pituitaries (NPs; n=12), using a microfluidic-based qPCR array. Our results revealed that several splicing machinery components and SFs were significantly altered in craniopharyngiomas from primary vs. recurrent surgeries and, in craniopharyngiomas vs. NP tissues. Interestingly, the expression of some splicing components was associated with key clinical characteristics. Altogether, these results suggest that some components of the splicing machinery and SFs might represent relevant diagnostic and/or prognostic tools and promising therapeutic target in craniopharyngiomas.

P39. Requirement of Cell-Of-Origin classification of DLBCL patients by gene expression profiling in NanoString technology from FFPET samples.

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Introduction: Diffuse large B-cell lymphoma(DLBCL)is an aggressive cancer and the most common non-Hodgkin's Lymphoma(NHL) in adult. Although new therapies have introduced significant improving of DLBCL, an important percentage of DLBCL patients remained with poor responses. Immunohistochemical(IHQ) algorithms labeling biomarkers such as Hans (BCL2, CD10, BCL6, and MUM1) which use standard formalin-fixed paraffin-embedded tissue(FFPET). This IHQ technic has poor association with prognostic outcomes increasing unclassified number of patients. Recently, studies base on "Lymphochip" complementary DNA(cDNA)open a new era for DLBCL cell-of-origin COO) classification being more precise than studios base on IHQ algorithms. Thus, a new GEP, successfully described a set of 20 genes for COO classification of DLBCL patients in germinal center B-cell-like (GCB) subtype and activated B-cell-like (ABC)subtype. Importantly, mutations in MYD88 gene have been associated with poor outcomes in ABC-DLBCL and were described in 29%of ABC-DLBCL with adverse prognostic.

Objectives: Firstly, we analyzed gene expression profiling of 27 DLBCL from FFPE samples by Nanostring technology for a rapid detection of high risk patients. Secondly, we detected L256P-MYD88 mutation in ABCgroup. Finally, we looked for statistical association with clinical variables.

Results: 48% of all DLBCL patients (13/27) were classified within GCB subtype,40%of them (11/27) had ABC molecular profile, and only 11%(3/27) were unclassified. However, when we applied Hans's IHQ algorism, based on Hans's markers, we obtained that 63%of the patients were classified within ABC and 33%belonged to GCB subtype. Thus, we found a 33%(8/27) of discrepancy between Hans and GEP algorisms, having an increased number of unreal ABC patients after Hans's algorithm. Besides, we did not find any statistical association with age, R-IPI, illness stage and other relevant clinical variables for this pathology. Finally, PCR studios reveled that 9%of all ABC patients carried L256P mutation at MYD88 gene.

Conclusions: Nanostring technology employs an array of 20 key genes allowing us to classify DLBCL precisely. Molecular subtype is independent for our clinical variables at diagnosis. Fast identification of ABC subtype and L256P-MYD88 mutation let the design of personalized treatments in this adverse group.

P40. Analysis of early recurrence in retroperitoneal Liposarcomas

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Background and objectives: The aim of this study is to identify factors involved in local recurrence in primary retroperitoneal liposarcoma.Patients and Methods: Prospective database of 35 patients with primary retroperitoneal liposarcoma treated between 2004 and 2015 were retrospectively analyzed. Exclusion criteria were recurrent and metastatic tumors. Overall survival and Disease-Free survival were reviewed. Patient data were compared between patients with or without recurrence within 12 months after surgery. Risk factors were determined using logistic regression analysis. Results: Five-year Overall Survival was 61.1%. One and three-year Disease-Free survival were 68.6% and 17.1% respectively. Overall survival in the early recurrence group was 36.4 months compared with 43.2 months in the group without early recurrence (p=0.011). Early recurrence was associated with a reduction in overall survival (HR=4.05; IC95% 1.27-12.96; p=0.018). Multifocality and microscopic positive margins R1 were associated with early recurrence. Histologic subtype, margin of resection, histologic grade and multifocality were factors associated with recurrence. Contiguously involved organ resection had a beneficial effect on early recurrence and was associated with an increase in Disease-free survival and Overall survival. Adjuvant treatments had no protective effect on recurrence.

Conclusions: This study underlines the crucial role aggressive surgical approach in retroperitoneal Liposarcoma treatment, especially in those patients with histological characteristics that adversely the prognosis.

P41. IMPACT OF PROGRESSION-FREE INTERVAL AFTER CHEMOTHERAPY PRE-SBRT IN OLIGOMETASTATIC PATIENTS

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PURPOSE: To check in our series whether progression-free interval after chemotherapy (PFIqt) pre-Stereotactic Body Radiotherapy (SBRT), could be a associated with local (LPFI), regional (RPFI) or distant (DPFI) progression-free interval, assuming the hypothesis that those patients considered as oligometastatic who take longer to progress after a systemic treatment will be better candidates to perform ablative treatments.
Secondarily, to know our results in terms of local control (LC), metastasis free survival (MFS) and overall survival (OS) in this cohort
MATERIAL AND METHODS: Fifty-five patients (82 metastases) were treated with SBRT after chemotherapy for advanced disease, and analyzed retrospectively between april 2011-november 2016.
The prescribed dose was 5x12Gy (76,8%) for peripheral lesions and 8x7,5Gy (23,1%) for central lesions. Local and regional control, and distant progression was evaluated by CT and PET/CT.
The Pearson correlation coefficient was calculated to evaluate the correlation between the PFI after pre-SBRT chemotherapy and the local, regional, and distance progression-free interval after SBRT.
The Kaplan-Meier analysis was used to estimate local, regional control, and distant-free survival.
RESULTS: The median follow-up period was 22,9 months (3,25-83,22). There were 36 men and 19 women with a mean age of 66 years (39-85). There wasn't a significant correlation between PFIqt and LPFI (R=0,3; p=0,77), RPFI (0,07; p=0,6) or DPFI (R=-0,07; p=0,6). There was a significant correlation between LPFI and RPFI (R=0,69; p<0,001) or DPFI (R=0,86; p<0,001)
LC at 2 years was 90%. MFS at 1 and 2 years were 68% and 57%. OS was 90% and 67% at 1 and 2 years respectively.
CONCLUSIONS: No linear correlation has been shown between PFIqt and time to local or regional progression or to distant metastases. The heterogeneity of our serie could explain our results.
Our results in terms of LC, MFS and OS are similar to those published in the literature.

P42. Regulation of SSTR5 expression and splicing in acromegaly by epigenetic and post-transcriptional events

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The somatostatin receptor 5 (SSTR5/sst5) and, particularly its truncated splicing variant sst5TMD4 are considered putative biomarkers for pharmacological response and aggressiveness in acromegaly. sst5TMD4 is generated by non-canonical splicing, but the mechanisms underlying its genesis are still unknown. Recent analyses revealed the existence of a natural antisense transcript, named SSTR5-AS1, which overlaps SSTR5 and may encode an intergenic long non-coding RNA that could regulate SSTR5 expression. Likewise, DNA methylation is also known to influence alternative splicing. Here, we implemented in silico and experimental analyses on SSTR5 and SSTR5-AS1 genes to explore the existence of CpG islands, placed at their promoters and coding regions. Our aim was to ascertain if these processes could regulate the expression or splicing of SSTR5 in acromegaly. Firstly, we measured mRNA levels of SSTR5, its variants and SSTR5-AS1 by qPCR in 11 normal pituitaries and 27 acromegaly samples. Additionally, we assessed the methylation status in four CpG areas of SSTR5 and SSTR5-AS1 genes. Results revealed that acromegaly samples expressed significantly more SSTR5 than normal pituitary, whereas no significant differences were found in the expression of SSTR5-AS1. Methylation analyses showed that CpG sites were differentially methylated on SSTR5 and SSTR5-AS1 genes in acromegaly compared with normal pituitary, which might explain the differential expression of SSTR5. Interestingly, mRNA levels of SSTR5-AS1 showed a direct correlation with SSTR5 expression, but not with splicing variants, both in acromegaly and normal samples. This suggests that the antisense may regulate the expression of the full-length SSTR5, without affecting its splicing variants. Altogether, our results support the notion that epigenetic and post-transcriptional events may contribute to regulate the expression of SSTR5 in acromegaly, while their precise involvement in SSTR5 splicing dysregulation remains to be defined.

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P43. Comprehensive study of non-functioning pituitary adenomas: in the search for biomarkers of tumor relapse

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Non-functioning pituitary-adenomas (NFPAs) comprise a group of heterogeneous tumors of the adenohypophysis defined by a lack of any functional hormonal hypersecretion which frequently imply a diagnosis delay. NFPAs do not effectively respond to pharmacological-treatment and are typically associated with considerable tumor masses causing severe comorbidities (e.g. headache/visual-defects/hypopituitarism). NFPAs frequently invade adjacent structures, preventing from a complete surgical-resection, which may lead to recurrence. However, to date reliable markers to predict tumor-relapse after surgery are not available for NFPAs. Therefore, in order to identify putative biomarkers for tumor relapse, we carried out a single-center observational retrospective study in 65 patients with NFPAs (2004-2017) with available pre-surgical clinical and radiological data, and with immunohistochemical (IHC) and molecular data after tumor-resection. Mean age was 61 (56% male); 40% presented headache; 67% visual defects. Total resection was achieved in 31% of cases, and 21% needed a second surgery due to the adenoma-recurrence. In 20% of cases, less than 50% of the tumor was resected due to the sinus-invasion features of these tumors. 81% affected optic-chiasm and the median tumor diameter was 27mm. Molecular data showed a predominant expression of the alpha-chain of glycoproteins (CGA) and gonadotropins compared to other pituitary-hormones, and a predominant expression of dopamine-receptor subtype-2 and somatostatin-receptor subtypes-3 and -2 compared to other key receptors, suggesting that NFPAs might be sensitive to dopamine/somatostatin-analogues treatment (i.e. octreotide/pasireotide/lanreotide and/or chimeric dopamine-somatostatin compounds). FSH and LH, but not p53 and ki67, levels were positively correlated at mRNA and IHC. Remarkably, tumors requiring a second surgery were significantly larger, p53/LH negative and presented low CGA/FSH mRNA levels, which may indicate an anaplastic condition. Altogether, our data indicate that the IHC and molecular phenotype evaluation of NFPAs may help to identify putative biomarkers for tumor-relapse and could contribute to the better understanding of the pathophysiology of aggressive NFPAs.

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P44. Automatic mapping and tracking of visual markers and camera rig localization for patient positioning in radiotherapy

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Patient positioning for radiotherapy, traditionally needs radiography of the patient to ensure the position of the tumor. Hence, it exposes the patient to ionizing electromagnetic waves at each session of the radiotherapy. New computer vision based approaches have been introduced in recent years for non invasive estimation of the tumor position. However these methods need expensive industrial level equipment.

Our ultimate goal is to design a vision based system for patient positioning that uses consumer-level cameras which are more affordable. To obtain high precision we aim to use visual fiducial markers attached to the patient (such as a bracelet with the markers attached on it) or the surrounding environment.

As a part of such a system, we have developed a fundamental algorithm that automatically maps the position of the fiducial markers with respect to each other, estimates the relative position of cameras (assuming their position does not change with respect to each other) and tracks the object with the fiducial planar markers attached to it. In our experiments we have been able to achieve high precision with low (VGA) resolution cameras.

P45. TARGETED REACTIVATION OF EPIGENETICALLY SILENCED GENES IN HUMAN CELLS USING A PLANT DNA GLYCOSYLASE AND CRISPR TECHNOLOGY

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DNA methylation is a stable but reversible epigenetic mark associated to gene silencing, and its targeted removal is a major goal of epigenetic editing. In human cells, passive demethylation involves iterative 5-methylcytosine (5-mC) oxidation by TET enzymes. However, although there is evidence to support the existence of active demethylation during development, the exact nature of this process is highly controversial and poorly understood. In contrast, plants use specific DNA glycosylases in DNA demethylation pathway to directly excise 5-mC and initiate its substitution for unmethylated C in a base excision repair process. The CRISPR methodology derives from a bacterial adaptive immune system that uses an RNA-guided nuclease (Cas9) to target and destroy invading DNA. The use of a catalytically inactive nuclease (dCas9) co-expressed with a short guide RNA (sgRNA) allows using CRISPR/dCas9 as a general platform for RNA-guided targeting of different epigenetic effector proteins to specific genomic regions. We have fused ROS1, a plant 5-mC DNA glycosylase, to dCas9 to achieve targeted active DNA demethylation and gene reactivation in human cells, tested on a luciferase reporter gene previously silenced by *in vitro* methylation. In contrast, neither DNA demethylation nor gene reactivation was observed with a dCas9-TET1 fusion protein.

To explore possible combinatorial effects inducing a synergic cooperation activity, dCas9-ROS1 was transiently co-transfected with additional effectors domains. However, no significantly improved DNA demethylation was found. Finally, different levels of DNA methylation at the reporter gene were tested for dCas9-ROS1-mediated DNA reactivation. Results show that reactivation potential depends on the initial methylation level at the target locus, which suggests that silencing induced by DNA methylation strongly depends on the level of 5-mC.

Altogether, these findings demonstrate the feasibility of using 5-mC DNA glycosylases and CRISPR/dCas9 technology for targeted active DNA demethylation and epigenetic editing.

POSTER SESSION II
Chronic and inflammatory diseases

P46. Comparative Study of Characterization and Determination of Immunomodulatory Efficacy of Bone Marrow-derived Mesenchymal Stem Cells expanded with Platelet Lysate or Fetal Bovine Serum supplemented medium.

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Introduction: Bone marrow-derived mesenchymal stem cells (BM-MSCs) represent an ideal tool for many cell-based therapies. Culture media used for *in vitro* expansion of BM-MSCs are currently being enriched with fetal bovine serum (FBS).
However, the use of FBS is being discouraged by drug regulatory agencies due to its xenogeneic compounds. In order to avoid the risks of contamination by FBS in clinical grade stem cell culture, human platelet lysate (PL) represents an efficient alternative to FBS for clinical-scale expansion of BM-MSCs.
Aim: In this study we have compared BM-MSCs expanded in culture media supplemented with FBS and PL in order to evaluate the effect upon BM-MSCs immunomodulatory activity, proliferation and secretion of paracrine factors. Additionally, we have evaluated cells function and phenotype under the different culture conditions.
Methods: BM-MSCs were isolated from bone marrow derived of healthy donors and expanded until passage two in culture media enriched with FBS or LP from two different manufacturing protocols. Cell phenotype and functional characterization were analyzed through flow cytometry and adipogenic and osteogenic differentiation capacity. BM-MSCs proliferation rates and cell morphology were performed by flow cytometry and immunomodulatory effects by co-cultivating BM-MSCs with peripheral blood mononuclear cells.
Results: BM-MSCs cultured with different supplemented media showed similar characteristics of surface marker expression and differentiation potential. BM-MSCs under PL supplemented culture conditions showed higher proliferation rates and they exhibited higher complexity and smaller size than BM-MSCs cultured under FBS conditions. Regarding immunomodulatory capacity, both were able to inhibit lymphocytes proliferation *in vitro*, however this effect was greater in BM-MSCs cultured with FBS.
Conclusion: BM-MSCs cultured under PL supplemented culture conditions increased proliferation rates and cell complexity, although their size and immunomodulatory capacity is slightly reduced when compared to BM-MSCs expanded under FBS conditions.

P47. Radiographic progression of patients with spondyloartritis after 13 years of follow up: data of regisponser.

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Observational analytical study of a retrospective cohort, in which 78 patients belonging to the REGISPONSER registry were analyzed, which were evaluated for the first time in the year 2004-2005. The last x-rays of the cervical spine, lumbar spine, pelvis and hips were recorded in the patients' medical records. For the calculation of the BASRI index, the radiographs recorded at the follow-up visit by two observers are evaluated independently and the interobserver concordance is studied using Cohen's Kappa statistic. Radiographic progression was assessed using the McNemar test.

Of the 78 patients included in the study, we had a radiographic study of 61 patients with an average of 11 (1.7) years from the baseline radiological examination, with a complete radiographic study (including cervical, lumbar, pelvic and hip spines) in 38 of them.

The strength of the interobserver concordance in the radiographic reading was almost perfect at the level of the cervical spine (k = 0.88, p <0.001), lumbar spine (k = 0.87, p <0.001), sacroiliac joints (k = 0.84, p <0.001).) and considerable in hips (k = 0.77, p <0.001) with a score of BASRIs 7.5 (2.9) and BASRIt 8.8 (4.1). There was an increase of BASRIt at 1.23 (p = 0.014) during the follow-up time.

We observed that 42.1% worsened in terms of the score corresponding to the cervical spine (p <0.001), 28.9% in the lumbar spine (p = 0.057), 15.8% in the hip (p = 0.754) and no worsening was found in sacroiliac (p = 0.500).

Analyzing the individual scores it seems that the cervical spine was the segment where there was greater radiographic progression. We did not find worsening of BASRI in sacroiliac due to the fact that the most of patients already had an advanced degree of sacroileitis in the first visit of the registry.

P48. Lactic acidosis as complication of metfomine use in diabetic patients

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INTRODUCTION: Metformin is the only biguanide currently available and produces lactic acidosis (LA) with an incidence of 9/100,000 habitants/year. The role of the metformin in the development of AL in patients with acute renal failure (ARF) is controversial.
The aim of the study was to assess a possible association in a cohort of patients with metformin that develop ARF.
METHODS: We analysed patients with metformin admitted for prerenal ARF in our department between 2010-2016 (n=77). We compared patients who had LA(n =46) with patients who did not present LA(n=31). We define LA as metabolic acidosis (pH<7.35) and lactate levels >5 mmol/l. We analyse the dose of metformin at the time of admission (<1g, 1-2g, >2g) and the clinical-analytical characteristics of the patients.
RESULTS: There was no significant difference in the basal characteristics. We find significant differences between both groups in the dose of metformin (p=0.036 <1g, p<0.000 1-2g and> 2g), taking other oral antidiabetics and presence of diarrhoea on admission. We perform a multivariate analysis. The results obteined show that the dose of metformin acts as an independent predictor of the development of LA (p<0.003). 55 patients required haemodialysis (HD) and 12 patients require admission to ICU. We found significant differences between both groups. Analysing the creatinine at the end of follow-up, patients with LA have higher levels compared to those who did not have AL
CONCLUSION: Our series shows a higher incidence than previously describe in the literature. These results demonstrate a strong association between the use of metformin and the presence of LA in diabetic patients with RFA. This association is dose dependent. Although patients with LA need more HD, admission in ICU and have worse renal function at the end of follow-up, there are not secondary factors of poor prognosis when the multivariate analysis is performed.

P49. Potentially avoidable hospital activity

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Introduction: In the current context of limited resources, it is of great interest to identify activities that could be avoided and that would allow to free resources for other purposes.
Several analytical approaches exist, both for hospitalizations and for visits to the emergency room, but there is no consensus regarding the indicators to be used.
Objectives:
- To quantify the potentially avoidable hospital activity in the Reina Sofía University Hospital of Córdoba.
- To describe the most frequent conditions in potentially preventable hospitalizations and emergencies.
Methods:
Descriptive study.
Data source: Hospital discharges of 2016.
Criteria for potentially avoidable activity: episodes of hospitalization that meet the criteria established by the AHRQ for the construction of Preventive Quality Indicators. To determine the potentially avoidable activity in the emergency room, the variable of the patient's origin (emergencies, consultations, etc ...) is analyzed.
Descriptive analysis of the potentially avoidable activity in hospitalization and emergencies are shown.
Results: During 2016 there were 38,024 hospitalizations, of which 3,211 (8.44%) were due to potentially avoidable conditions. In 2,892 of the cases (90.07% of the PQI cases), the origin of the patients was emergencies. Emergencies attended during 2016 were 189,581, and potentially avoidable cases represent 1.53% of emergency attendances.
The main causes of potentially avoidable care were: Heart Failure, Pneumonia and COPD / Asthma.
Conclusions: Approximately 8.5% of the hospital admissions and 1.5% of the emergencies attended in 2016 were due to potentially avoidable ambulatory care conditions in the out-of-hospital setting, either due to: a) prevention of the onset of the disease, b) treatment of acute diseases or c) control of chronic diseases. This type of analysis allows to guide preventive actions that, in our case, should focus on a better management of: Heart Failure, Pneumonia and COPD / Asthma

P50. Physical activity in nursing students at the University of Cordoba

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Background: Physical exercise provides physiological, psychological and social benefits. In Spain, between 20% and 39% of the persons do not perform physical exercise. Physical exercise is related to absence or less drug use. Objective: To find out the characteristics of physical activity in undergraduate nursing students. Methods: Observational descriptive study. Subjects and scope of study: University Nursing students between 18-30 years old, University of Cordoba (Spain). Sample: 84 subjects, 21 per course. Variable: practice of physical activity. Instrument: questionnaire for the health information areas (Pastor et al., 2009). Report from the Research Ethics Committee of Córdoba. Information and Informed Consent Form. Data analysis: χ^2 test with qualitative data, analysis of variance with quantitative. A $p < 0.05$ was considered. Results: 76.2% of nursing students practice physical exercise, 23.8% do not practice it. In relation to physical exercise according to sex, 88.9% of men and 72.7% of women perform physical exercise. In relation to the type of physical exercise more than half of students practice resistance activity (54.7%), 31.3% practice two or more types of physical exercise. After passing through the university, 35.7% of students practice more physical exercise. With regard to the course, in the first year 14.3% practice more physical exercise, and in the last year 46.7%. Conclusions: Nursing students at the University of Cordoba have a high physical activity practice rate, slightly higher than the practice of university students to other studies. Men practice more physical exercise. Students on their last year practice more physical exercise than during their first year.

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P51. Validation of Berlin questionnaire for the detection of 40-year-old patients who suffer from sleep apnea hypopnea syndrome

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Introduction: Sleep Apnea-Hypoapnea Syndrome (SAHS) is a clinical picture with multiple comorbidities and complications; such as hypertension blood pressure, waketime sleepiness and cardiovascular events. Usually it is not diagnosed. The Gold Standard is polysomnography, which is expensive and unavailable. Berlin questionnaire is used like screening method, but there is no validated version in Spain

Objective: Validate Berlin questionnaire like a diagnostic method of SAHS in Spanishh people, who attends to primary health care. It is pretended to know the differences between men and women; to know the prevalence and quality of life of these patients as a secundary objective. Final del formulario

Material and Methods: It is a descriptive observational study with a preliminary qualitative phase of transcultural adaptation to Spanish language, which is used to detect SAHS in Spanish population around 40 years old or more. The sample size has been calculated in based on the initial review. This one had a prevalence of 8.5%, sensitivity 86%, specificity 77%, accuracy of 10% and an estimation of confidence interval: 95%. On the basis of the above, it is concluded that the simple size is 553 patients. Recruitment will be done by consecutive sampling. Sociodemographic and clinical variables will be measured. Berlin Questionnaire will be filled by the patients; moreover, a polygraph will be carried out. In the borderline case, a polysomnography will be done too. Information sources: digital data collection notebook and DIRAYA digital medical history. In addition, a descriptive analysis will be done in order to know of these patients. We will make a bivariate analysis, later. Sensitivity, specificity, predictive values and the ROC curve will be calculated to measure criterion validity. The internal consistency degree will be calculated through Cronbach's alpha. The reason why Cohen's Kappa index will be calculated is to measure the intraobserver concordance. All these estimators will be expressed with their 95% confidence intervals. The statistical package SSPS version 22 and the EPIDAT program version 3 will be carried out, so that these calculations can be done.

ETHICAL-LEGAL ASPECTS:

This project will adapt to the current legislation (LOPD, Ley de Investigación). The informed consent will be requested to each subject. It will be sent for its approvement to the Research Ethics Committee. Authorization will be requested to the Management / Directorate of the Sanitary District Córdoba and Guadalquivir

P52. Conscientiousness, subjective well-being and cardiac self-efficacy on health perception of cardiovascular patients

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Cardiovascular disease constitutes the main chronic disease, in terms of prevalence and morbidity worldwide. For this reason, the main research objective consists to analyze some psychosocial variables associated to the development of health-related quality of life of patients with cardiovascular disease across time evaluations. The sample included 514 patients (mean age 63.57). All participants answered a questionnaire which assessed the level of conscientiousness, perceived subjective well-being –positive and negative affect, and life satisfaction-, cardiac self-efficacy, and health-related quality of life. All psychosocial variables measured established a conceptual causal model of starting. The results of the structural equation modeling (SEM) analyses [χ^2 (46, *N* = 514) = 145,029, *p* = .000; *GFI* = ; *AGFI* = .918; *CFI* = .956; *RMSEA* = .065, 95% *CI* [.053, .077)] indicated that conscientiousness, subjective well-being, and cardiac self-efficacy had a longitudinal effect on the final health-related quality of life evaluated. Meanwhile, mediation analyzes explain the relationships between variables proposed in a significant way, where positive affect, life satisfaction, cardiac self-efficacy and self-assessment health had a direct impact on final health-related quality of life. The results obtained indicate the necessity to the promotion psychosocial interventions to increase the diary positive affect situations and the perception of cardiac self-efficacy to improve the perception of health-related quality of life of cardiac patients.

P53. Evolving Nuss Technique. A single center experience.

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Objectives: To review the evolving technique of minimally invasive repair of pectus excavatum (PE) performed at our institution over a 17-year period.
Methods: Retrospective review of all PE patients undergoing surgical repair by the Nuss Procedure from January 2001 to December 2017. Demographic, surgical and postoperative variables were recorded and compared between early era (from 2001 to 2012) and late era (from 2013 to 2017). Groups were defined according to main changes in operative technique (surgical approach, number of stabilizers and chest drains). Non-parametric tests were used for comparisons.
Results: 65 patients (20±7 yrs; 59M/6F) were included. 4 patients had a perceived limitation of exercise ability, 5 presented a progression after a Ravitch procedure, and the remaining 56 underwent surgery for cosmetic reasons. Comparative analysis (early – 30 patients vs. late – 35 patients): Age (21±8 vs 18±5; p=0.15), gender (M/F) (28/2 vs 31/4; p=ns), Haller Index (9.4±9 vs 3.8±1, p=0.07), early complications (10 vs 2, p=0.005; pneumothorax 4 vs 1p=0.13; haemothorax 2 vs 0 p=0.21; bar displacement 3 vs 1, p=0.25, other 2 vs 0, p=0.46); mean bar duration (2.3 vs 2.1 years p=0.8); hospital stay (7±4 vs 4±1 days, p=0.004); cosmetic results (excellent/good/poor) (25/3/2 vs 33/2/0, p=0.23). Neither fatal complications nor PE recurrence after bar removal were recorded.
Conclusions: The Nuss procedure is a safe and effective technique to repair PE deformities. The experience gained over time in our Institution allowed us to lessen the invasiveness and reduce complications with excellent long-term results.

P54. Preferential usage patterns of methodological quality and bias risk assessment tools: A meta-epidemiological study of 20,000 PROSPERO records of non-Cochrane systematic reviews

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Background: Epidemiology and the reporting characteristics of systematic reviews (SRs) and meta-analyses (MAs) are well known. However, descriptive analyses of a priori registration records published at the International Prospective Register of Systematic Reviews (PROSPERO) rare scarce. Objective: To describe usage patterns of methodological and bias risk tools included in non-Cochrane registration records for systematic reviews and meta-analyses.
Methods/Design: Methods to conduct this meta-epidemiological study were published by our group in an a priori protocol. The PROSPERO repository web was scraped by iteratively running custom Python script to obtain all completed non-Cochrane registration records stored from February 2011 to December 2017. Manual and human-supervised automatic methods were used for data extraction. The tools for bias risk assessment, year of record submission, country, number of reviewers, CIE-10 code for topic, and nature of review were obtained. R and Python programming and analysis languages were used to describe the datasets, perform text mining, and visualize the data.
Results: Downloaded records were screened and those with less than 90% fulfilled or are duplicated (i.e., those sharing titles and reviewers) were excluded. As a result, 20,272 full non-Cochrane registration records were obtained (25.3%), of which only 20,146 were finally included in the analyses. The tool for bias risk assessment was only defined in 10,656 (52.89%) protocols. The most frequently mentioned tools were the Cochrane Risk of Bias tool for Randomized Controlled Trials (2,163; 20.3%), the Newcastle-Ottawa scale (1,901; 17.9%), and the GRADE Cochrane's recommended approach for grading the quality of evidence and the strength of recommendations (1,014; 9.5%). Most of the protocols which included any tool were from England (1,716; 16.1%), Australia (1,074; 10%), and Canada (1,004; 9.4%); Spain was found in the #10 position.
Conclusion: This meta-epidemiological study has explored, for the first time, the preferential usage of methodological quality and risk of bias assessment tools of PROSPERO records to conduct non-Cochrane systematic reviews.

POSTER SESSION II
Infectious and Inmunological diseases. Organ transplantation

P55. Factors associated with the exacerbation of tuberculosis

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The Exacerbation of tuberculosis (TB) is defined as the diagnostic of one recurrence from TB you cause by reinfection in patients who previously are been for tuberculosis, followed completed treatment at the end of the last cycle of treatment.

From the perspective of public health, the tuberculosis has been continuing a significative worldwide problem. Ecuador is one of the countries with median burden of tuberculosis that holds the 10th position in Latin america with an estimated incidence of 33.75 x 100.000 habitants.

Objective: to analyze the factors associated with the recurrence of patients with tuberculosis.

Methodology: Analytical observational study of cohorts in patients diagnosed with tuberculosis. Cohort exposed to risk factor (TB factor) and non-exposed cohort (TB without factor). Recurrences will be collected in each group. This project will be developed from March 2018 to March 2021, in two districts of the Ecuadorian coast of Manabi and Guayas. Data collection: through a specific survey factors related to the patient (nutritional status, empowerment, instruction, occupation, income), their illness and treatment. Statistical analysis: measure of the causal association through the Relative Risk. Significance (chi square) will be determined and the confidence limits for 95% (95% CI) of the main study estimators will be calculated.

Previous Results: reactivate a specialized program, which will include the nutritional aspect that allows to reduce the risk factors to prevent the spread of the disease, contribute to a better control in patients with tuberculosis and avoid the relapse of the patients. Measures will be taken to guarantee treatment, reinforcing the model of health care in Ecuador. Health professionals who research patients can contribute to self-care and improve the quality of life in this type of culture.

P56. Prognosis of ventilator-associated respiratory tract infection caused by colistin-resistant KPC*Klebisella pneumoniae* with high-level meropenem resistance.

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Background. It is not well known the prognosis of the ventilator-associated respiratory tract infection caused by KPC carbapenemase-producing Klebsiella pneumoniae (KPCKp)
Objective: To assess whether the ventilator-associated respiratory tract infection caused by a KPC-Kp strain is associated with poorer outcome than carbapenemsusceptible isolates.
Methods. This is a retrospective observational study of patients with ventilator associated respiratory tract infections due to K. pneumoniae. An adjusted multivariable analysis was used to study the association of KPC-Kp with 30-day all-cause mortality (Cox regression) and clinical-microbiological cure (logistic regression).
Results. We analyze 74 cases of K. pneumonia ventilator-associated respiratory tract infections of which 42 were produced by a colistin-resistant KPC-Kp strain with high level of resistance to meropenem. The KPC-Kp etiology was not associated with higher mortality (adjusted HR, 1.08, 95% CI, 0.4-2.91) or lower clinical cure-microbiology (OR 0.76, 95% CI 0.21-2.61).
Conclusions Assuming the limitations derived from the available sample size,
ventilator-associated respiratory tract infection by KPC-Kp was not associated with a worse prognosis than those caused by meropenem sensitive strains.

P57. Epidemiology of antimicrobial resistance in bloodstream infections caused by *Enterobacteriaceae* in solid organ transplant patients: the INCREMENT-SOT Study.

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INTRODUCTION: Antimicrobial resistance in bacterial pathogens is a worldwide challenge leading to high morbidity and mortality in clinical settings. In recent years, infections by *Enterobacteriaceae* producing extended-spectrum β-lactamase (ESBL-E) and /or carbapenemase (CPE) have emerged as a global threat in solid-organ transplant (SOT) patients. The INCREMENT-SOT Project is a multinational, observational, retrospective study aimed at evaluating the impact of specific antimicrobials and MIC values on the outcome of bloodstream infections due to ESBL-E or CPE in SOT patients (BSI-SOT). A secondary objective involved the generation of a microbial collection of multidrug-resistant enterobacteria (MDRE) associated with the BSI-SOT episodes retrospectively collected for the clinical study. Here, we present the preliminary results for the molecular and epidemiological characterization of this MDRE collection.

METHODS: Isolate identification was performed by MALDI-TOF (Brucker System). Minimum inhibitory concentrations (MICs) of β-lactams, quinolones, aminoglycosides, fosfomycin, tigecyclin and colistin were determined by broth microdilution or gradient strips, and interpreted using CLSI clinical breakpoints. ESBL production was confirmed using tests based on the inhibition of ESBL by clavulanic acid. Carbapenemase-production was confirmed through the modified carbapenemase-inactivation method (mCIM). Molecular detection of resistance genes was performed for carbapenemase genes. Clonal relatedness was assessed by Rep-PCR.

RESULTS: A total of 189 MDRE isolated from BSI-SOT patients in 14 international hospitals were studied. 145/189 (76.7%) were ESBL-producers, 40/189 (21.2%) were CPE and 4/189 (2.1%) were ESBL+CPE. The most represented species were *K. pneumoniae* (48.1%, among which 58% were ESBL producers and 42% were CPE), *E. coli* (43.9%) and *E. cloacae* (4.8%). Among the 44 CPE isolates, specific carbapenemase genes were identified in 19 (43.2%) isolates: OXA-48 in 9/44 (20.5%), KPC in 6/44 (13.6%), GES in 3/44 (6.8%) and VIM in 1/44 (2.3%) isolates.

Conclusion: *E. coli* producing ESBL was the most prevalent MDRE, followed by *K. pneumoniae* harboring ESBL or carbapenemase genes.

P58. Should be included the universal screening for hepatitis e virus Infection in blood donors? Results from central spain

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Background: Spanish Hepatitis E virus (HEV) Guidelines and European Centre for Disease Prevention and Control establish that the decision to screen blood donations for HEV should be determined by the background prevalence of transmissible infection in the donor population and the susceptibility of recipients.
Aim: To evaluate the prevalence of HEV infection in blood donors form central Spain.
Methods: It was included in the study blood donations from healthy donors collected in Ciudad Real (Central Spain) between September 2017 and January 2018. Serum samples were analyzed for HEV using nucleacid testing methods, in pools of 8 samples.
RNA was extracted using QIAcube (QIAgen, Hilden, Alemania), and tested by RT-PCR amplifying the ORF3 viral region using an in-house method (CFX Connect Real Time PCR System. Biorad, Hercules, California). Positive pools were tested and quantified
individually using LightCycler 480 (Roche, Basel, Switzerland). An external in run standard curve was applied to calculate HEV viral load using the WHO HEV standard strain supplied by the Paul-Ehrlich-Institut (code 6329/10), consistent with genotype 3a. Viral load was expressed as IU/mL. It was calculated the prevalence of HEV infection.
Results: A total of 6,097 donations were included in the study. We identify 4 samples positive for HEV. This supposed a prevalence of 0.06% or one in 1,519 donations.
These sample were from 4 different patients. Viral loads were, 2 million IU/mL, 43,000 IU/mL, 10,000 IU/mL, and 2,800 IU/mL, respectively. All viral isolated were consistent with genotype 3.
Conclusions: Our study show a high HEV infection prevalence among blood donors form Central Spain. Our data suggest that the risk for HEV transfusion-transmitted HEV could be important in our setting.

P59. Bacterial load as risk factor for colonization, dissemination to the community and mortality by carbapenemase-producing Klebsiella pneumoniae: KLEBCOM study.

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BACKGROUND: The spread of Klebsiella pneumoniae carbapenemase (KPC)-type enzymes has led to the emergence of carbapenem-resistant Enterobacteriaceae (CRE), mostly K. pneumoniae, as important nosocomial pathogens. Asymptomatic, intestinal colonization with CRE is a known risk factor for subsequent CRE infection. We studied the quantification of rectal colonization in asymptomatic carriers of KPC-producing CRE by calculating the ratio of CRE colony forming units (CFU) or blaKPC gene copies to an appropriate reference, representing other gut flora. We aim to determine if the relative CRE load in these patients is a predictive risk factor for crude mortality, infection, colonization and dissemination to caregivers.
METHODS: Observational, prospective cohort study. Three cohorts: colonized patients (PAC), caregivers (CON), decolonized patients (DIS). 1-year follow-up. Bacterial load determined by culture-based method (CRE to total aerobic CFU ratio or CRE/TAB) and quantitative real-time PCR (blaKPC /16S rRNA gene copies).
RESULTS: 14 patients (9 PAC and 5 DIS) were recruited from February to April 2018. Median (IQR) age was 85 (70-88). 10 (71.4%) of patients were female. 9 (64.3 %) had 1 or more admissions to hospital in the previous 6 months. At day 0 and 40 of follow-up, PAC patients showed median (IQR) CRE/TAB ratios (as percentage) of 13.41% (0.02%-63.7%) and 3.87% (0%-17.1%), respectively. Among 5 DIS patients CRE/TAB was 14.25% (3.66%-75.21%) at day 0. Two DIS patients died before completing decolonization. The other 3 showed KPC-CRE eradication at day 14 post-DIS and 2,1%, 3,36% and 1.8 % CRE/TAB ratios at day 40 post-DIS.
CONCLUSIONS
Rectal swabs are appropriate for quantifying KPC-producing CRE load. Preliminary results from the DIS cohort show that KPC-CRE decolonization leads to KPC-CRE eradication at the end of therapy, however this reduction in bacterial load is temporary in a number of patients, who become recolonized over time.

POSTER SESSION II
Active ageing and fragility

P60. The motivation in the students of training cycles

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Objectives: The objective of this study is to know and analyze the existing scientific production on the level of motivation and influential factors in the students of the Training Cycles.

Method: A limited systematic search was conducted in the REDIB and Dialnet databases during the month of March 2018. Period 2005-2017. The search was carried out with the following terms: motivation & training cycles, motivation & professional training, motivation & secondary compulsory studies. The studies were selected according to the following inclusion criteria: scientific studies that presented as variables the motivation of the students belonging to the Training Cycles and factors that influenced said motivation.

Results: 8 articles met the inclusion criteria. Studies have been found mainly related to the practices in companies that had to make the students of the Training Cycles once they had passed the theoretical contents. The students showed a high motivation to perform these practices. The variables related to its usefulness for professional training, the development of work and their perception of their future job insertion reached a higher percentage compared to aspects related to ICT and the resources of the workplace where the degree of motivation had been lower. Also, the training in work centers increases the motivation and the interest to study in the university and work in the profession for which they were being trained. In conclusion, the author consider that not enough evidence about the topic has been found; so it is necessary to increase the research in others Index to find it.

P61. Impact of nutritional interventions on the liver of mice overexpressing CYB5R3 and its influence on apoptosis and coenzyme Q system

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Several interventions have been reported to delay aging and attenuate a wide variety of diseases associated with this process. Among them, calorie restriction without malnutrition (CR), is the most effective nongenetic intervention that promotes a healthy aging phenotype and extends lifespan. CR increases the amount of monounsaturated fatty acids in membranes while decreasing polyunsaturated fatty acids (PUFA) without any observed changes in saturated fatty acids, which is in accordance to the Theory of Membranes in Aging, given the different susceptibility to oxidative damage exhibited by these fatty acids. Based on this theory and the Free Radical Theory of Aging, it follows that variation of the predominant dietary fat source emerges as a valuable tool to modulate redox balance and the levels oxidative damage. In this way, interventions that do not only attenuate oxidative damage but are also capable of decrease PUFAs content in membranes might have anti-aging benefits as observed in individuals subjected to CR. On the other hand, studies focused on the identification of novel enzymes with the ability to modulate aging are starting to emerge. Previous studies developed in our group were focused on NADH-cytochrome b_5 reductase-3 (CYB5R3) as a new pro-longevity gene. Mice that overexpress this protein showed increased longevity and displayed greater protection against diseases associated with aging process. However, how RC and fat source variations interact in CYB5R3-overexpressing mice, and its role in the modulation of cell metabolism are largely unknown. Based on this, to gain new insights into the physiological role of CYB5R3 in aging, we developed an *in vivo* mouse model overexpressing CYB5R3. Our main aim was to determine how CYB5R3 transgenic mice respond to nutritional interventions using liver as model of study. We have payed especial attention towards those proteins involved in apoptosis and to the pathways that regulate metabolism and CoQ system.

P62. Chronobiological patterns and sex differences in serious falls of independent elderly people

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Background: Time of fall is a critical epidemiology variable, since it has been shown fall events do not occur at random, but rather there exist "windows" during the 24h, week, and year when they are more likely. We studied temporal patterns of serious community falls independently living seniors.
Methods: Serious falls (requiring admission to the hospital emergency unit services) in community-dwelling elderly (≥65 yrs old) experienced in 2013, in a city of southern Spain, were studied prospectively. Sociodemographic data, medical history, circumstances of fall were studied. Time series analysis (Cosinor analysis) was used.
Results: Falls were ~3-fold more common in women than men, and ~7-fold more frequent between ~12:00 and 14:00h than at ~02:00h -- the major peak and trough of the 24-hour pattern. A second less prominent peak was manifested in the evening between ~18:00 and 22:00h. The high-amplitude day/night pattern of female and male fallers differed. Overall, findings suggest the midday peak of community falls primarily involves women ≥75 years when inside-the-home due to an accident while walking, standing, or moving on stairs. The late evening somewhat less prominent excess of incidents is primarily representative of inside-the-home falls of women of the same age caused by fragility, slip, stumble, or tripping. Day-of-week patterning, with prominent Thursday peak and Sunday minimum, was also detected, but only for outside-the-home falls of women (Cosinor analysis: P=0.007). Non-statistically significant month-of-year disparity in falls, lowest in autumn and highest (~60% more) in winter, was observed, explained by seasonal discrepancy in the number of falls by women.
Conclusion: Twenty-four-hour, weekly and annual patterns in serious falls of independent senior were found. Chronobiological patterns differ according to gender.

P63. High Risk Antenatal Clinic and monitoring ambulatory blood pressure in pregnancy: an Italian pilot study

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Background: Blood pressure (BP) is clearly defined by Ambulatory BP monitoring (ABPM). BP is strongly related to target organ damage and vascular risk. The High Risk Antenatal Clinic (HRAC) at the General Hospital of Ferrara, Italy, has been established to improve the prenatal results of high risk pregnant women. The aim of the study was to review the impact of a collaborative diagnostic pathway at this single center, offering ABPM in HRAC pregnant women.
Methods: We included all pregnant women evaluated at HRAC between 2012 and 2016, recorded in the local database. We analyzed demographic and clinical characteristics including overweight, presence of fetal complications, type of delivery, miscarriage or abortion, gestational age and weight of the baby at the time of delivery, prescription of ABPM and changes in anti-hypertensive treatment.

Results: We included 395 pregnant women aged 33.9 ± 5.6 years, firstly seen when gestational age was 19.6±9.6 weeks. ABPM was carried out at the following gestational age: 19 ± 8, 22 ± 8, 26 ± 8 week and beyond. A single ABPM procedure was performed in 87 cases (22%), and multiple in 100 cases (25%). In at least one third of cases of single measurement, ABPM was followed by medical intervention aimed to modify the pre-existing therapeutic treatment. Decision tree analysis suggested that hypertension and overweight were the main reasons for performing ABPM
Conclusion: Results of this pilot study suggested that ABPM could be considered a helpful method able to help in establishing BP values in obese pregnant women and in anti-hypertensive prescription.

P64. Sexual dysfunctions in the postpartum: a systematic review

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INTRODUCTION: Sexual dysfunctions in women have a significant impact on health and quality of life. The postpartum is a period in which alterations in the sexual sphere can occur due to the type of delivery, perineal injuries caused by it, stress and fatigue generated by the new family role. The objective of the study is to know the available evidence on sexual dysfunctions in the postpartum and determine what factors are involved in these alterations.
METHODOLOGY: Systematic review. An electronic search was performed in the first half of April using the following databases: MEDLINE, Ovid SP, Web of Science. The keywords used were: "Sexual Dysfunction" AND "Postpartum Period". Articles whose subject matter was related to sexual dysfunction after childbirth were included. Those articles related to dysfunctions in other stages or pathologies were excluded. A descriptive and categorical thematic analysis were carried out (most prevalent sexual dysfunctions and risk factors).
RESULTS: 48 articles met the inclusion criteria. Of these, one was a systematic review, six cross-sectional studies, two cross-sectional comparative studies, a longitudinal study, two observational longitudinal cohort studies, nine prospective studies of which one was follow-up and another observational, two longitudinal cross-sectional cohorts, nine prospective cohort studies and four cohort studies, a prospective follow-up study of a randomized comparative trial, two prospective longitudinal studies, two randomized control trials, seven questionnaire-based studies and two randomized control trials.
CONCLUSIONS: The probability of suffering a dysfunction in the postpartum is high. The most frequent alterations are dyspareunia, sexual desire disorder, and orgasmic alterations. The type of delivery and injuries in the perineum and pelvic musculature negatively influence the sexual health of the woman. Other factors involved are breastfeeding, stress, postpartum depression, and previous pathologies such as diabetes, hypothyroidism, obesity and epilepsy.

POSTER SESSION II
Nutrition, Endocrine and metabolic diseases

P65. The alpha-cell dysfunction may precede type 2 diabetes: from the CORIDOPREV study.

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Background: Type 2 diabetes mellitus (T2DM) is an expanding global health problem that parallels the epidemic of obesity and encompasses a high risk of cardiovascular complications. Many studies have been focused on the relationship between the beta-cell dysfunction and the T2DM or prediabetes pathophysiology, but the role of alpha-cell has been neglected. However, both alpha- and beta-cells dysfunction are implicated in the development of type 2 diabetes mellitus (T2DM). We aimed to evaluate whether alpha- and beta-cell dysfunction may precede prediabetes (PreDM) and T2DM development.
Materials and methods: This study was conducted in the population of the CORDIOPREV study (1002 patients), of which 462 patients had not T2DM at baseline. During the follow-up period, 107 patients developed T2DM (T2DM-incident), 30 developed PreDM (PreDM-incident) and 29 patients remained without PreDM or T2DM criteria (control group), according to the American Diabetes Association diagnosis criteria. We measured glucose, insulin, glucagon and GLP-1 plasma levels in the oral glucose overload (OGTT) performed at baseline and after 2 years of follow-up.
Results: We observed higher levels of GLP1 in the PreDM-incident group as compared with the control group ($p=0.025$), whereas T2DM-incident subjects showed an intermediated response. We found higher levels of glucagon and the glucagon/insulin ratio (G/I) in the T2DM-incident group compared with PreDM-incident and control groups after an OGTT at baseline and after 2 years of follow-up ($p<0.05$). T2DM Risk Assessment by COX analysis using G/I ratio at 30 min after an OGTT was able to assess the T2DM risk with an HR of 2.514.
Conclusion: Our results suggest that alpha-cell dysfunction precedes the T2DM development, and the consequent high glucagon levels may accelerate the beta-cell exhausting to counteract the insulin action. Also, our results support the potential of G/I ratio in the OGTT as a predictor factor in assessing T2DM development risk.

P66. Rab34 as a biomarker of lipid droplet remodelling in 3D models of obesity and hepatic steatosis

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In obesity, the excessive storage of lipids in the adipocytes and fibrosis promote adipose tissue dysfunction and the resulting lipid spillover contributes to the development of hepatic steatosis. We recently demonstrated the presence of the Rab GTPase, Rab34, as a constituent of the lipid droplet (LD) proteome of adipocytes. It has been shown that Rab GTPases associate with the Golgi apparatus to undergo prenylation, which allows them to anchor to their target membranes wherein they become activated. Thereafter, Rabs can separate from membranes and deactivate, behaving like molecular switches. Notably, we have shown that Rab34 remains bound to the Golgi in undifferentiated adipocytes and fasting hepatocytes, and migrates to the surface of LDs as soon as they are formed during adipogenesis or in hepatocytes upon fatty acid overload. Thus, herein we employed Rab34 as a model molecule in order to unveil Rab routing to LDs through the Golgi apparatus as well as its role on LD dynamics. First, the structure of human Rab34 was inferred using 3D-molecular-modeling tools, which revealed the topological characteristics contributing to Rab34 targeting to LDs. Rab34 overexpression and silencing studies in *in vitro* models of obesity and hepatic steatosis showed a role for this protein in LD biogenesis in both adipocytes and hepatocytes. Notably, confocal microscope visualization of human mature adipocytes cultured in 3D matrices (Matrigel) showed that the Golgi-LD transition of Rab34 occurs through the ERGIC/ERES compartment (Endoplasmic-Golgi intermediate compartment/Endoplasmic-Reticulum Exit Sites). Finally, culture of adipocytes in 3D matrices with increasing stiffness revealed impaired accumulation of LDs together with changes in Rab34. Altogether, our results support a role for Rab34 in the incorporation of lipids into the LDs of adipocytes and hepatocytes, thus representing a potential target for obesity and hepatic steatosis.

P67. Study of sample preparation for determination of endocannabinoids and analogous compounds in human serum by LC–MS/MS in MRM mode

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Endocannabinoids are endogenous mediating lipids with a key role in physiological processes such as the immune response or the metabolism. This involvement explains their association to several pathologies such as cancer, obesity, schizophrenia or multiple sclerosis. In fact, altered levels of anandamide and 2-arachidonoyl glycerol in blood have been found in patients with obesity or schizophrenia. Their determination constitutes a challenge for clinical laboratories owing to the wide range of concentrations at which they can be found. Traditional sample preparation protocols are based on lipids extraction, by leaching solid samples (mainly brain tissue) and liquid-liquid extraction/protein precipitation for serum and plasma samples. Typically, the extracts are subjected to a clean-up step by solid-phase extraction (SPE) to remove interferents. Methods based on gas- or liquid chromatography (GC or LC, respectively) coupled to mass spectrometry (MS or MS/MS) have been mainly used for determination. The aim of this study was to develop an analytical method able to quantify 14 endocannabinoids in human serum by online coupling SPE to LC–MS/MS. The proposed method was compared with other approaches based on the same determination method but with different sample treatments. One of them was based exclusively on protein precipitation while the other one included a SPE step for selective elimination of glycerophospholipids. The method reported here allows full automation of the overall process, which involves a shortening of the analysis time and avoidance of errors associated with sample preparation steps. The improvement in sensitivity and selectivity leads to quantification limits at the pg mL^{-1} levels, which makes possible the application of the method to clinical studies.

P68. Diet-regulation of miRNAs involved in the development of atherosclerosis in patients with cardiovascular disease

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Background: Cardiovascular diseases are the primary cause of death worldwide. The common base of these diseases is atherosclerosis, a process characterized by the thickening of the carotid intima-media. Dietary intervention is a tool to prevent the development of atherosclerosis and to reduce the risk of cardiovascular diseases. Previous studies have demonstrated the role of miRNAs in atherosclerosis-related mechanisms. Our aim was to study the modulation by diet of miRNAs involved in the progression and regression of carotid intima-media thickness (cIMT) as a risk factor in the development of atherosclerosis in patients with established cardiovascular disease.

Materials and Methods: Patients with established cardiovascular disease participating in the CORDIOPREV study were selected according to progression and regression of cIMT after 5 years of intervention with low fat or Mediterranean diets: cIMT progression + low fat (n=58), cIMT progression + Med (n=62), cIMT regression + low fat (n=51), and cIMT regression + Med (n=69). Carotid intima-media thickness was measured bilaterally with high-resolution B-mode Doppler echography. Intracellular expression of miRNAs from peripheral blood mononuclear cells was measured at baseline and after 5 years of follow-up using the OpenArray platform.

Results: Our results show that miR-21 expression was higher in cIMT progression + Med and lower in the cIMT regression + low fat group after 5 years of follow-up compared to baseline (p= 0.036 and p= 0.004, respectively). Moreover, miR-429 expression was lower in cIMT progression + Med group after the follow-up period compared to baseline (p= 0.025).The expression of miR-31 decreased in cIMT progression groups after consumption of both diets (cIMT progression + low fat group, p= 0.001 and cIMT progression + Med group, p= 0.02).

Conclusion: The dietary intervention could regulate the expression of miRNAs directly involved in mechanisms associated with atherosclerosis development in patients with cardiovascular disease.

P69. GLUCOGENE: Diabetes risk prediction at 2 years for coronary patients on dietary advice (from the CORDIOPREV Study).

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Background: To develop optimized prediction models for new onset diabetes mellitus type 2 (T2DM) on coronary patients.
Methods: All coronary patients without previous T2DM (n=462) from the CORDIOPREV clinical trial were followed for two years for T2DM development. We generated and tested different statistical models (versus FINDRISK calculation) to identify future patients of T2DM upon 2 different statistical approaches (classification models and logistic regression). These models were built to be used with different sets of information (Base, Extended, Enhanced and Full).
Results: 79 patients (17.1%) developed new onset T2DM. Best C-statistic coefficients with the two set of models were: Regression models 0.92 (Sensitivity 0.91, Specificity 0.80); Classification models 0.65 (Sensitivity 0.56, Specificity 0.74). Logistic regression models reached higher ROC curves than mean of Classification models, and they improved as we enriched the set of variables (Base < Extended < Enhanced < Full), improving the prediction rates of FINDRISK (C-statistics 0.55, Sensitivity 0.82, Specificity 0.28).
Conclusions: Regression models showed more effective that classification models, and achieved a higher ROC for prediction accuracy. These models are adaptable to the known parameters of a patient, and improve the sensitivity and ROC curve of the standard method (FINDRISK) in the CordioPrev study.

P70. Beneficial effect of two healthy diets in the damage and regenerative capacity processes of the endothelium: CORDIOPREV study.

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Our aim was to determine whether consumption of two models of healthy diets produces a differential effect in damage and regenerative capacity processes of the endothelium in patients with cardiovascular heart disease (CHD). From the total patients of CORDIOPREV study (NCT00924937) (n = 1002), we selected 24 patients: 12 patients with the lowest values of flow-mediated dilation of the brachial artery (FMD<2%, severe endothelial dysfunction) and 12 patients the highest values of FMD (FMD>4.5%, normal endothelial function. In each group and for a period of one year, 6 patients consumed a Mediterranean diet and 6 patients consumed a low-fat diet. We carried out *in vitro* studies using two models of endothelial cells [Human Umbilical Vein Endothelial Cells (HUVECs) and Endothelial Progenitor Cells (EPCs), incubated with the serum (10%) of these patients. We evaluated endothelial damage [reactive oxygen species (ROS) and apoptosis in HUVECs and cellular senescence in EPCs) and endothelial regenerative capacity [cellular proliferation and angiogenesis in EPCs].

- Mechanisms related to endothelial damage: Mediterranean diet reduced the intracellular production of ROS in patients with severe endothelial dysfunction. However, the low-fat diet increased its levels independently of the degree of endothelial dysfunction. On the other hand, the consumption of low-fat diet increased cellular apoptosis in both groups of patients but Mediterranean diet produced lower levels of apoptosis that the low-fat diet.
- Mechanisms related to endothelial repair: Mediterranean diet increased angiogenesis process (determined by total length of the master segments and the number of unions in both groups of patients.

Our data suggest that consumption of a Mediterranean diet, but not a low-fat diet, improves endothelial dysfunction in patients with coronary heart disease, even in those at higher risk (with severe endothelial dysfunction). These findings highlight the possibility of establishing therapeutic dietary strategies that, by reducing endothelial damage and increasing regenerative capacity, lead to an improvement in endothelial dysfunction with the aim of reducing the increased risk of CVD in these patients.

P71. In the search of adipose tissue biomarkers responsive to surgery-induced weight loss. A SWATH-MS proteomic approach.

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Bariatric surgery (BS) is currently recognised as the most effective treatment for obesity and obesity-associated metabolic disease, yet the mechanisms by which BS improves adipose tissue (AT) functionality are not fully understood. In order to identify potential BS-responsive targets, a comparative SWATH-MS proteomic analysis of subcutaneous adipose tissue (SAT) samples (n= 14) from morbidly obese subjects obtained during BS (pre-BS) and approximately 1 year after (post-BS) was carried out. SWATH analysis identified 156 proteins to have significantly different expression post-BS, of which 107 were upregulated and 49 downregulated. Mitochondrial pathways were the major biological processes up-regulated post-BS, specifically fatty acid β-oxidation and the tricarboxylic acid cycle, which is consistent with weight loss-induced improvements in the metabolic profile of the patients. These changes were more noticeable in those patients with lower obesity duration. In line with the proteomic data, RT-PCR studies revealed BS-induced changes in markers of adipose tissue browning. Another pathway that appeared to be responsive to BS was endoplasmic reticulum (ER) stress, as indicated by the down-regulation of the ER chaperone, BiP, in SAT samples 1-year after surgery. This was also associated to changes in components of the ER-associated degradation (ERAD) pathway, including proteins involved in the retrotranslocation of misfolded proteins from the ER to the cytosol. As for mitochondrial pathways, dissimilar regulation of the ERAD was observed depending on the duration of obesity. In sum, our data point to the mitochondria as central players in the functional recovery of the adipose tissue in response to BS. In particular, increased fatty acid metabolism together with ER function normalisation, may contribute to the beneficial effects of BS, at least in those patients with short-standing obesity, suggesting that the benefits of BS are more pronounced the earlier obesity is treated.

P72. Is our self-perception determined by genes or the environment? A pilot study

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Introduction: The fact that people use social networks such as Facebook, Twitter or Instagram for large amounts of time has become an indisputable reality. These networks have become the most common form of sociocultural interaction for young people who are prominent as the most addicted users.
The influence of social networks and its effect on young people's self-image has been studied in previous studies. However, the influence that has this technology not only produce a bad self-image or decrease in the self-stem, but indeed, produce several changes in the personality of a person, especially young people.
Objective: This study first explored the relationship between self-stem, social networks, 2D:4D ratio, eating disorder, loneliness, social networks addiction, body dissatisfaction and reflex.
Methods: The data (N=33) was obtained of a survey made of EAT-26, ARS, CIPE-a, ESTE II y BSQ surveys and photographs from students of the biological, nursing and education degrees. The relationship between quantitative variables was studied using the Pearson's correlation coefficient. The data were studies using SPSS® packed version 22 and the program GeoGebra®.
Results: The results show diverse relationships between the studied variables: the age is related with the social networks importance (p-value=0.009) and self-stem (p=0.033); the eating disorder is related with body satisfaction (p=0.002), method to obtain the image desire (p=0.002), self-stem (p=0.11) and loneliness (p=0.035); the 2D:4D difference is related with the self-stem (p=0.004) and self-perception (p=0.029).
Conclusion: The variable which value shows a higher correlation with the rest of the variables, is the eating disorder

P73. TYPE 1 DIABETES AT SCHOOL.

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Objective: To know how type 1 diabetes affects the school environment.

Material and method: Bibliographic review of the scientific literature made in Pubmed and ProQuest following the PRISMA modified criteria during November and December 2017. Considering as inclusion criteria those articles that were elaborated in the last decade and free access; excluding those which do not use English or Spanish. Finally of 101, a total of 17 articles were selected.

Results: It is estimated that approximately half of a child's vigil hours are spent in school, under the care of teachers and other school staff. But, when we talk about children with type 1 diabetes, we have to talk about the importance of preparing these professionals to manage the disease. Few schools have access to trained health professionals to help providing training before emergencies that can trigger diabetes in the classroom. Diabetes Mellitus type 1 is associated with a slightly lower cognitive capacity and less learning difficulties. Acute episodes of glycemic alterations will temporarily affect the mental state of the parents, making them being alert and living with a continuous fear of the possible adverse effect. That is why the main sources of information are the parents, causing them the appearance of symptoms of burn-out, often associated with the feeling of the impact of their daily lives.

Discussion: The lack of communication between teachers and families makes clear a large gap in the family-school partnership. Parents' concerns about insufficient support in self-care received at school are independent at the child's age.

Conclusions: In the school environment, type 1 diabetes conditions children who suffer from it, so schools must be prepared for the unexpected situations and it is recommended to adopt action plans to help school personnel to act in an emergency situation.

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